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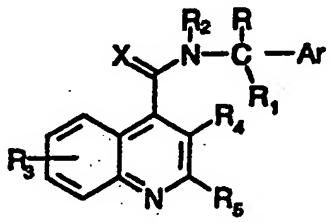
(54) Title: QUINOLINE DERIVATIVES AS TACHYKININ NK_3 RECEPTOR ANTAGONISTS

(57) Abstract

NK_3 receptor antagonists of formula (I) are useful in treating *inter alia* pulmonary disorders, CNS disorders and neurodegenerative disorders.



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QUINOLINE DERIVATIVES AS TACHYKININ NK3 RECEPTOR ANTAGONISTS

The present invention relates to novel quinoline derivatives, processes for their preparation and their use in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognises the other two receptors with lower affinity (Maggi et al , 1993, *J. Auton. Pharmacol., 13*, 23-93).

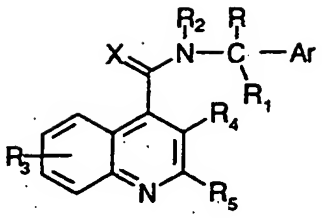
Selective peptidic NK_3 receptor antagonists are known (Drapeau, 1990 *Regul. Pept.*, 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, J.Phisiol., 470, 665-679; Counture et al., 1993, Regul. Peptides, 46, 426-429; Mccarson and Krause, 1994, J. Neurosci., 14 (2), 712-720; Arenas et al. 1991, J.Neurosci., 11, 2332-8).

However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

We have now discovered a novel class of selective, non-peptide NK_3 antagonists which are far more stable from a metabolic point of view than the known peptidic NK_3 receptor antagonists and are of potential therapeutic utility in treating pulmonary disorders (asthma, chronic obstructive pulmonary diseases -COPD-, airway hyperreactivity, cough), skin disorders and itch (for example, atopic dermatitis and cutaneous wheal and flare), neurogenic inflammation and CNS disorders (Parkinson's disease, movement disorders, anxiety and psychosis). These disorders are referred to hereinafter as the Primary Disorders.

The novel NK_3 antagonists of the present invention are also of potential therapeutic utility in treating convulsive disorders (for example epilepsy), renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression (hereinafter referred to as the Secondary Disorders).

According to the present invention there is provided a compound, or a solvate or salt thereof, of formula (I):



(I)

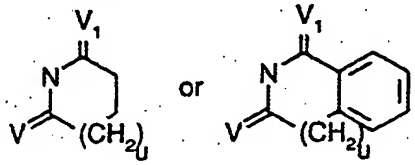
in which:

Ar is an optionally substituted phenyl, naphthyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted phenyl or phenyl C_{1-6} alkyl, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatom selected from O and N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or is a group $-(CH_2)_p-$ when cyclized onto Ar, where p is 2 or 3.

R_1 and R_2, which may be the same or different, are independently hydrogen or C_{1-6} linear or branched alkyl, or together form a -(CH2)n- group in which n represents 3, 4, or 5; or R_1 together with R forms a group $-(CH_2)_q-$, in which q is 2, 3, 4 or 5.

R_3 and R_4, which may be the same or different, are independently hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, mono- and di-C_{1-6} alkylamino, $-O(CH_2)_r-NT_2$, in which r is 2, 3, or 4 and T is hydrogen or C_{1-6} alkyl or it forms with the adjacent nitrogen a group



in which V and V_1 are independently hydrogen or oxygen and u is 0,1 or 2;

$-O(CH_2)_s-OW_2$ in which s is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl;

hydroxyalkyl, aminoalkyl, mono-or di-alkylaminoalkyl, acylamino,

alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleus;

or R_4 is a group $-(CH_2)_t-$ when cyclized onto R_5 as aryl, in which t is 1, 2, or 3;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

X is O, S, or N-C≡N.

Examples of Ar are phenyl, optionally substituted by hydroxy, halogen, C_{1-6} alkoxy or C_{1-6} alkyl. Examples of halogen are chlorine and fluorine, an example of C_{1-6} alkoxy is methoxy and an example of C_{1-6} alkyl is methyl.

Examples of Ar as a heterocyclic group are thienyl and pyridyl.

Examples of Ar as a C_{5-7} cycloalkdienyl group is cyclohexadienyl.

Examples of R are as follows:

C_{1-8} alkyl: methyl, ethyl, n-propyl, iso-propyl, n-butyl, heptyl;

phenyl C_{1-6} alkyl: benzyl;

hydroxy C_{1-6} alkyl: - CH_2OH, $-CH_2CH_2OH$, CH(Me)OH;

amino C_{1-6} alkyl: $-CH_2NH_2$;

di C_{1-6} alkylaminoalkyl: $-CH_2NMe_2$;

C_{1-6} alkoxylalkyl: CH_2OMe;

C_{1-6} alkylcarbonyl: COMe;

C_{1-6} alkoxycarbonyl: COOMe;

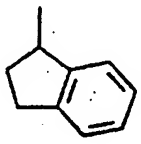
C_{1-6} alkoxycarbonyl C_{1-6} alkyl: CH_2COOMe;

C_{1-6} alkylaminocarbonyl: CONHMe;

di C_{1-6} alkylaminocarbonyl: $CONMe_2$, CO(1-pyrrolidinyl);

halogen C_{1-6} alkyl: trifluoromethyl;

$-(CH_2)_p-$ when cyclized onto Ar:



Example of R_1 and R_2 as C_{1-6} alkyl is methyl;

example of R_1 together with R forming a group $-(CH_2)_q-$ is spirocyclopentane.

Examples of R_3 and R_4 are methyl, ethyl, n-propyl, n-butyl, methoxy, hydroxy, amino, chlorine, fluorine, bromine, acetyloxy, 2-(dimetylamino)ethoxy, 2-(1-phthaloyl)ethoxy, aminoethoxy, 2-(1-pyrrolidinyl)ethoxy, phthaloyl, dimethylaminopropoxy, dimethylaminoacetylamino, acetylamino, dimethylaminomethyl and phenyl.

Examples of R_5 are cyclohexyl, phenyl optionally substituted as defined for

Ar above; examples of R_5 as a heterocyclic group are furyl, thienyl, pyrryl, thiazolyl, benzofuryl and pyridyl.

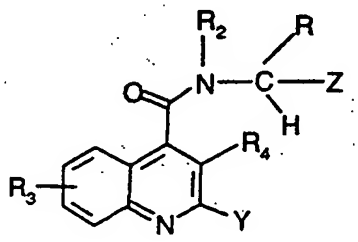
A preferred group of compounds of formula (I) are those in which:

Ar is phenyl, optionally substituted by C_{1-6} alkyl or halogen; thienyl or a C_{5-7} cycloalkdienyl group;
R is C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl;
R_1 and R_2 are each hydrogen or C_{1-6} alkyl;
R_3 is hydrogen, hydroxy, halogen, C_{1-6} alkoxy, C_{1-6} alkyl;
R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, halogen, aminoalkoxy, mono- or di-alkylaminoalkoxy, mono- or di-alkylaminoalkyl, phthaloylalkoxy, mono- or di-alkylaminoacylamino and acylamino;
R_5 is phenyl, thienyl, furyl, pyrryl and thiazolyl.

A further preferred group of compounds of formula (I) are those in which:

Ar is phenyl, 2-chlorophenyl, 2-thienyl or cyclohexadienyl;
R is methyl, ethyl, n-propyl, -COOMe, -COMe;
R_1 and R_2 are each hydrogen or methyl;
R_3 is hydrogen, methoxy, or hydroxy;
R_4 is hydrogen, methyl, ethyl, methoxy, hydroxy, amino, chlorine, bromine, dimethylaminoethoxy, 2-(1-phthaloyl)ethoxy, aminoethoxy, 2-(1-pyrrolidinyl)ethoxy, dimethylaminopropoxy, dimethylaminoacetylamino, acetylamino, and dimethylaminomethyl.
R_5 is phenyl, 2-thienyl, 2-furyl, 2-pyrryl, 2-thiazolyl and 3-thienyl;
and X is oxygen.

A preferred sub-group of compounds within the scope of formula (I) above is of formula (Ia):

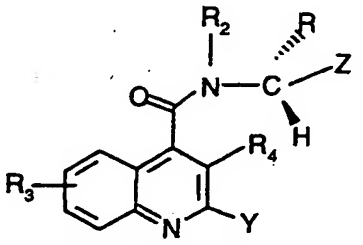


(Ia)

in which:

R, R_2, R_3 and R_4 are as defined in formula (I), and Y and Z, which may be the same or different, are each Ar as defined in formula (I).

A particularly preferred group of compounds of formula (Ia) are those of formula (Ib) in which the group R is oriented downward and H upward.



(Ib)

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

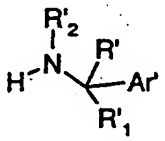
One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salts of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic, and methanesulphonic.

Examples of pharmaceutically acceptable solvates of a compound of formula (I) include hydrates.

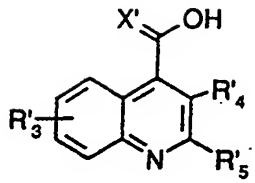
The compounds of formula (I) may have at least one asymmetric centre and therefore may exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

The invention also provides a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (III)



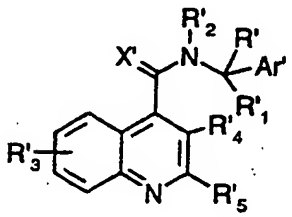
(III)

in which R', R'_1, R'_2 and Ar' are R, R_1, R_2 and Ar as defined for formula (I) or a group or atom convertible to R, R_1, R_2 and Ar, with a compound of formula (II)



(II)

or an active derivative thereof, in which R'3, R'4, R'5 and X' are R_3, R_4, R_5 and X as defined for formula (I) or a group convertible to R_3, R_4, R_5 and X, to form a compound of formula (Ic)



(Ic)

and optionally thereafter performing one or more of the following steps:

(a) where R', R'1 to R'5, Ar' and X' are other than R, R_1 to R_5, Ar and X, converting any one of R', R'1 to R'5, Ar' and X' to R, R_1 to R_5, Ar and X to obtain a compound of formula (I),

(b) where R', R'1 to R'5, Ar' and X' are R, R_1 to R_5, Ar and X, converting any one of R, R_1 to R_5, Ar and X to another R, R_1 to R_5, Ar and X, to obtain a compound of formula (I),

(c) forming a salt and/or solvate of the obtained compound of formula (Ic).

Suitable active derivatives of the compounds of formula (II) are acid halides (preferably chlorides), acid azides or acid anhydrides. Another suitable derivative is a mixed anhydride formed between the acid and an alkyl chloroformate; another suitable derivative is an activated ester such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; or the carboxy group may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

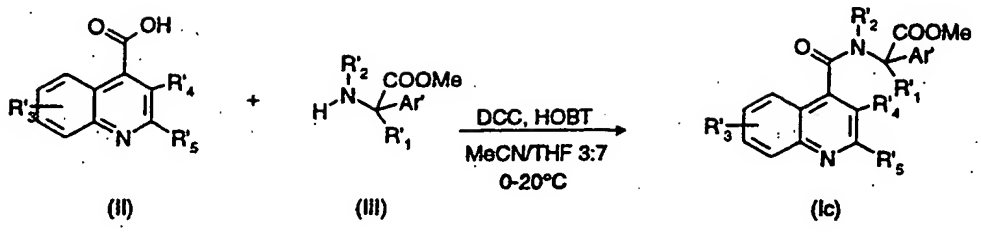
For example, in standard methods well known to those skilled in the art, the compounds of formula (III) may be coupled:

(a) with an acid chloride in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a

range from -70 to 50°C (preferably in a range from -10 to 20°C),

(b) with the acid in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide and N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (*Synthesis*, 453, 1972) in an aprotic solvent such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF) in a ratio from 1 : 9 to 7 : 3, respectively, at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 25°C) (see Scheme 1),

Scheme 1



(II) (III) (Ic)

(c) with a mixed anhydride generated in situ from the acid and an alkyl (for example isopropyl) chloroformate in a suitable aprotic solvent such as dichloromethane at a temperature in a range from -70 to 50°C (preferably in a range from -20 to 20°C).

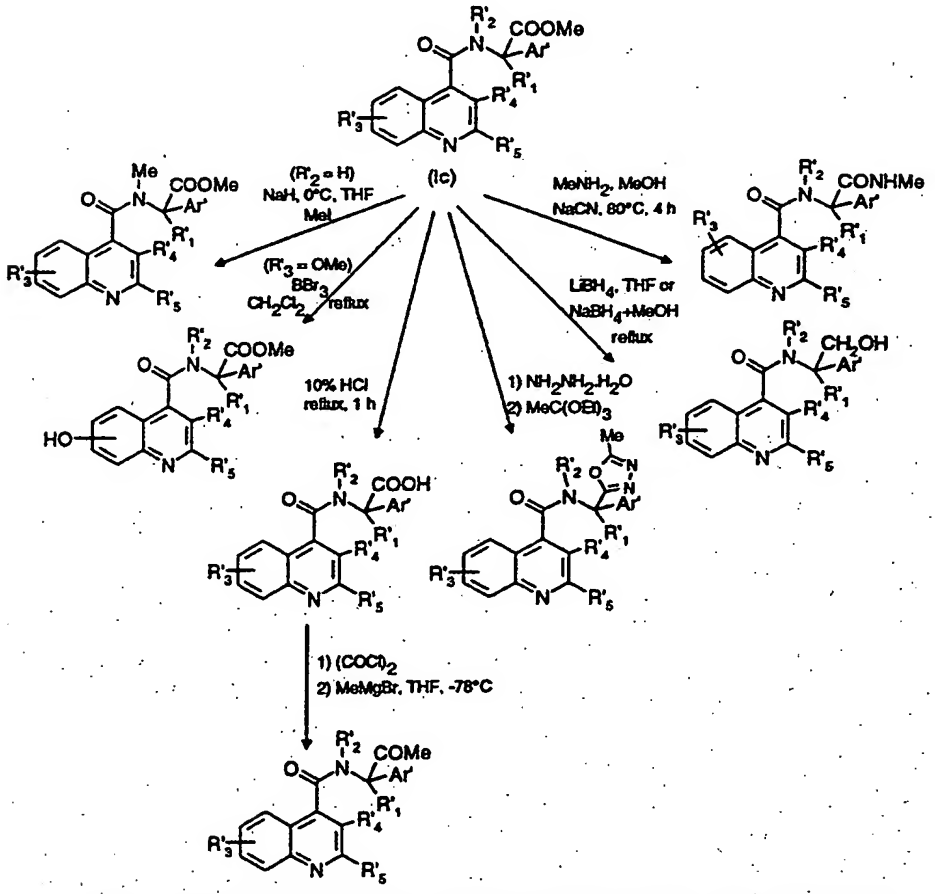
It will be appreciated that a compound of formula (Ic) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I), by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ic) are useful intermediates in forming other compounds of the present invention.

For example R'_2 may be hydrogen and converted to R_2 alkyl group, for example methyl, by conventional amide alkylation procedures (Zabicky, *The chemistry of amides*; Interscience, London, 1970, p. 749). When X' is oxygen, it may be converted to X sulphur by standard thioamide formation reagents, such as P_2S_5 (*Chem. Rev., 61*, 45, 1961 or *Angew. Chem., 78*, 517, 1966) or the Lawesson reagent (*Tetrahedron, 41*, 5061, 1985). When Ar' or R'_5 is a methoxy substituted phenyl, it may be converted to another Ar' or R'_5 hydroxy substituted phenyl by standard demethylation procedures via Lewis acids, such as boron tribromide (*Synthesis*, 249, 1983) or mineral acids, such as hydrobromic or hydroiodic acid. When R is an alkoxycarbonyl group, for example methoxycarbonyl, it may be converted to another R, such as ethoxycarbonyl by transesterification with an appropriate alcohol at a temperature in a range from 20 to 120°C, carboxy by hydrolysis in acidic or basic medium, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl by transamidation with ammonia, a primary amine or a secondary amine in methanol as solvent at a temperature in a range from 10 to 120°C, optionally in the presence of a catalytic amount of NaCN (*J. Org. Chem., 52*, 2033, 1987) or by using trimethylaluminium (Me_3Al) (*Tetrahedron Letters, 48*, 4171, 1977), hydroxymethyl by a selective metal hydride reduction, such as lithium borohydride reduction (*Tetrahedron, 35*, 567, 1979) or sodium borohydride reduction in THF + MeOH (*Bull. Chem. Soc. Japan, 57*, 1948, 1984 or *Synth. Commun., 12*, 463, 1982), alkylcarbonyl by acyl chloride formation and subsequent reaction with alkylmagnesium halides in THF as solvent at

a temperature in a range from -78 to 30°C (*Tetrahedron Letters*, 4303, 1979) or with alkylcadmium halides or dialkylcadmium in the presence of $MgCl_2$ or LiCl (*J. Org. Chem.*, *47*, 2590, 1982). Another group which R' as methoxycarbonyl can be converted into is a substituted heteroaromatic ring, such as an oxadiazole (*J. Med. Chem.*, *34*, 2726, 1991).

Scheme 2 summarizes some of the above described procedures to convert a compound of formula (Ic) or (I) in which X' is oxygen, R' is COOMe, Ar' and R'_1 to R'_5 are as described for formula (I) to another compound of formula (I).

Scheme 2



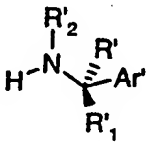
The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example, hydrates may be formed

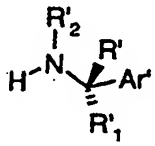
by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

As mentioned before, the compounds of formula (I) may exist in more than one stereoisomeric form and the process of the invention may produce racemates as well as enantiomerically pure forms. To obtain pure enantiomers, appropriate enantiomerically pure primary or secondary amines of formula (IIId) or (IIIe)

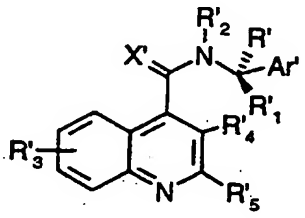


(IIId)



(IIIe)

are reacted with compounds of formula (II), to obtain compounds of formula (I'd) or (I'e).



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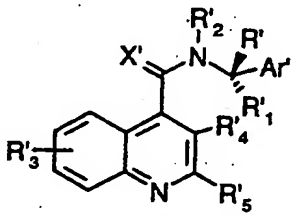
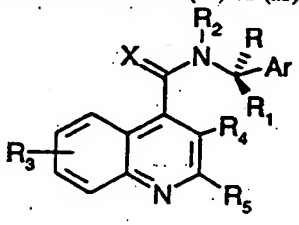
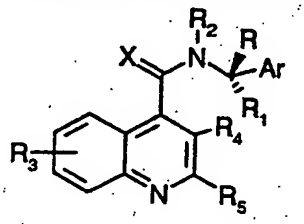


(I'e)

Compounds of formula (I'd) or (I'e) may subsequently be converted to compounds of formula (Id) or (Ie) by the methods of conversion mentioned before.



(Id)



(Ie)

Compounds of formula (II) are known compounds or can be prepared from known compounds by known methods.

For example, the compound of formula (II), in which X' is oxygen, R'3, R'4

and R'_5 are hydrogen is described in Pfitzinger, *J. Prakt. Chem., 38,* 582, 1882 and in Pfitzinger, *J. Prakt. Chem., 56,* 293, 1897; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is 2-pyridyl is described in Risaliti, *Ric. Scient., 28,* 561, 1958; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *o*-, *m*- and *p*-chlorophenyl, *o*-fluorophenyl and 3,4-dichlorophenyl are described in Brown *et al., J. Am. Chem. Soc., 68,* 2705, 1946; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-methoxyphenyl is described in Ciusa and Luzzatto, *Gazz. Chim. Ital., 44,* 64, 1914; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *m*-trifluoromethylphenyl is described in Shargier and Lalezari, *J. Chem. Eng. Data, 8,* 276, 1963; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-fluorophenyl is described in Bu Hoi *et al., Rec Trav. Chim., 68,* 781, 1949; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-methylphenyl is described in Prevost *et al., Compt. Rend. Acad. Sci., 258,* 954, 1964; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-bromophenyl is described in Nicolai *et al., Eur. J. Med. Chem.*, 27, 977, 1992; the compound of formula (II) in which X' is oxygen, R'_4 and R'_5 are hydrogen and R'_3 is 6-methyl is described in Buchmann and Howton, *J. Am. Chem. Soc., 68,* 2718, 1946; the compound of formula (II), in which X' is oxygen, R'_4 and R'_5 are hydrogen and R'_3 is 8-nitro is described in Buchmann *et al, J. Am. Chem. Soc., 69,* 380, 1947; the compound of formula (II), in which X' is oxygen, R'_4 is hydrogen, R'_3 is 6-chloro, R'_5 is p-chlorophenyl is described in Lutz *et al., J. Am. Chem. Soc., 68,* 1813, 1946; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is 2-thiazolyl is described in **Eur. Pat. Appl. EP 112,776**; compounds of formula (II), in which X' is oxygen, R'_3 is 8-trifluoromethyl, R'_4 is hydrogen and R'_5 are phenyl, *o*- and *p*-fluorophenyl, 3,4-dichlorophenyl, *p*-methoxyphenyl are described in Nicolai *et al., Eur. J. Med. Chem.*, 27, 977, 1992; compounds of formula (II), in which X' is oxygen, R'_3 is 6-bromo, R'_4 is hydrogen and R'_5 are phenyl or *p*-fluorophenyl are described in Nicolai *et al., Eur. J. Med. Chem.*, 27, 977, 1992; other compounds of formula (II) are described in **Ger. Offen. DE 3,721,222** and in **Eur. Pat. Appl. EP 384,313**.

Compounds of formula (III), (IIId) and (IIIe) are commercially available compounds or can be prepared from known compounds by known methods (for example, compounds of formula (III) in which R' is alkoxycarbonyl, R'_1 and R'_2 are hydrogen and Ar' is as defined for the compounds of formula (I), are described in *Liebigs Ann. der Chemie, 523,* 199, 1936).

The activity of the compounds of formula (I) as NK_3 receptor antagonists in standard tests indicates that they are of potential therapeutic utility in the treatment of

both the Primary and Secondary Disorders herein before referred to.

The discovery that NK_3 receptor antagonists have potential therapeutic utility in treating the Secondary Disorders is new, and in a further aspect of the present invention there is provided the use of an NK_3 receptor antagonist for the treatment of the Secondary Disorders. There is also provided the use of an NK_3 receptor antagonist in the manufacture of a medicament for the treatment of any of the Secondary Disorders.

The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Disorders.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may

contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid

form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention further provides a method for the treatment and/or prophylaxis of the Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of an NK_3 receptor antagonist.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, [^{125}I]-[Me-Phe^7]-NKB or [^{3}H]-Senktide, to guinea-pig and human NK_3 receptors

(Renzetti et al, 1991, *Neuropeptide, 18*, 104-114; Buell et al, 1992, *FEBS, 299(1)*, 90-95; Chung et al, 1994, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).
The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe^{7}]-NKB and [^{3}H]-Senktide specific binding to NK_3 receptor in equilibrium conditions (IC_{50}). Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 1-1000 nM; in particular, in guinea-pig cortex membranes by displacement of [^{3}H]-Senktide, the compounds of the Examples 22, 47, 48, and 85 display K_is (nM) of 5.6, 8.8, 12.0 and 4.8 respectively (n=3). The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, 1990, *Br. J. Pharmacol., 101*, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., 1991, *Eur. J. Pharmacol., 199*, 9-14) and human NK_3 receptors-mediated Ca^{++} mobilization (Mochizuki et al, 1994, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K_B value of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.
The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

The following Descriptions illustrate the preparation of the intermediates, whereas the Examples illustrate the preparation of the compounds of the present invention. The compounds of the Examples are summarised in the Tables 1 to 6

DESCRIPTION 1

2-phenylquinoline-4-carboxylic acid chloride

11.7 ml (136.3 mmol) of oxalyl chloride were dissolved in 150 ml of CH_2Cl_2. The solution was cooled at -10°C and 20 g (80.2 mmol) of commercially available 2-phenylquinoline-4-carboxylic acid were added portionwise. The reaction mixture was left overnight at room temperature and then evaporated to dryness to yield 22 g of the title compound, used without further purification.

$C_{16}H_{10}ClNO$

M.W. = 267.76

DESCRIPTION 2

7-methoxy-2-phenylquinoline-4-carboxylic acid

5 g (28.2 mmol) of 6-methoxyisatin, 4 ml (33.8 mmol) of acetophenone and 5.2 g (92.6 mmol) of potassium hydroxide were dissolved in 22.9 ml of abs. EtOH and the slurry heated at 80°C for 42 hours. After cooling of the reaction mixture, 50 ml of water were added and the solution extracted with 50 ml of Et_2O. The ice-cooled aqueous phase was acidified to pH 1 with 37% HCl and the precipitate collected by filtration and washed with water.

The solid obtained was dried *in-vacuo* at 40°C to yield 7.0 g of the title compound.

$C_{17}H_{13}NO_3$

M.P. = 226-228°C

M.W. = 279.30

Elemental analysis: Calcd. C,73.11; H,4.69; N,5.01;
Found C,72.07; H,4.59; N,4.90.

I.R. (KBr): 3420; 1630 cm^{-1}.

DESCRIPTION 3

7-methoxy-2-phenylquinoline-4-carboxylic acid chloride

2.8 ml (32.3 mmol) of oxalyl chloride were dissolved in 60 ml of CH_2Cl_2. The solution was cooled at -10°C and 6 g (19.0 mmol) of 7-methoxy-2-phenylquinoline-4-carboxylic acid were added portionwise. The reaction mixture was left overnight at room temperature and then evaporated to dryness to yield 7 g of the title compound, used without further purification.

$C_{17}H_{12}ClNO_2$

M.W. = 297.74

DESCRIPTION 4

7-hydroxy-2-phenylquinoline-4-carboxylic acid hydroiodide

1.5 g (5.4 mmol) of 7-methoxy-2-phenylquinoline-4-carboxylic acid were added portionwise to 50 ml of 57% aqueous HI. The reaction mixture was refluxed and vigourously stirred for 5 hours; then it was evaporated *in-vacuo* to dryness to yield 2.1 g of the title compound.

$C_{16}H_{11}NO_3$. HI

M.W. = 393.17

I.R. (KBr): 3120; 1650; 1620 cm^{-1}.

DESCRIPTION 5

2-(2-thienyl)quinoline-4-carboxylic acid

5 g (34.0 mmol) of isatin, 4.4 ml (40.8 mmol) of 2-acetylthiophene and 6.3 g (112.2 mmol) of potassium hydroxide were dissolved in 40 ml of abs. EtOH and the slurry heated at 80°C for 16 hours. After cooling of the reaction mixture, 50 ml of water were added and the solution extracted with 50 ml of Et_2O. The ice-cooled aqueous phase was acidified to pH 1 with 37% HCl and the precipitate collected by filtration and washed with water.

The crude product obtained was dried *in-vacuo* at 40°C and triturated with EtOAc to yield 4.8 g of the title compound.

$C_{14}H_9NO_2S$

M.P. = 181-183°C

M.W. = 255.29

I.R. (KBr): 1620 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 8.60 (d, 1H); 8.45 (s, 1H); 8.10 (m, 2H); 7.78 (m, 2H); 7.68 (t, 1H); 7.22 (m, 1H).

DESCRIPTION 6

2-(2-furyl)quinoline-4-carboxylic acid

5 g (34.0 mmol) of isatin, 4 ml (40.8 mmol) of 2-acetylfuran and 6.3 g (112.2 mmol) of potassium hydroxide were dissolved in 40.9 ml of abs. EtOH and the slurry heated at 80°C for 12 hours. After cooling of the reaction mixture, 50 ml of water were added and the solution extracted with 50 ml of Et_2O. The ice-cooled aqueous phase was acidified to pH 1 with 37% HCl and the precipitate collected by filtration and washed with water. The crude product obtained was dried *in-vacuo* at 40°C to yield 8.5 g of the title compound.

$C_{14}H_9NO_3$

M.W. = 239.23

DESCRIPTION 7

2-(2-furyl)quinoline-4-carboxylic acid chloride

5.2 ml (60.4 mmol) of oxalyl chloride were dissolved in 70 ml of CH_2Cl_2. The solution was cooled at -10°C and 8.5 g (35.5 mmol) of 2-(2-furyl)quinoline-4-carboxylic acid were added portionwise. The reaction mixture was left overnight at room temperature and then evaporated to dryness to yield 9.2 g of the title compound, used without further purification.

$C_{14}H_8ClNO_2$

M.W. = 257.78

DESCRIPTION 8

2-(4-pyridyl)quinoline-4-carboxylic acid hydrochloride

5 g (34.0 mmol) of isatin, 4.5 ml (40.8 mmol) of 4-acetylpyridine and 6.3 g (112.2 mmol) of potassium hydroxide were dissolved in 40 ml of abs. EtOH and the slurry heated at 80°C for 12 hours. After cooling of the reaction mixture, 50 ml of water were added and the solution extracted with 50 ml of Et_2O. The ice-cooled aqueous phase was acidified to pH 1 with 37% HCl and the precipitate collected by filtration and washed with water.

The aqueous solution was evaporated *in-vacuo* to dryness, the residue triturated with EtOH and filtered off. Evaporation of the solvent afforded 6.0 g of the crude title compound. This product was combined with the previously obtained precipitate and recrystallized from toluene containing traces of MeOH to yield 4.5 g of the title compound.

$C_{15}H_{10}N_2O_2 . HCl$

M.P. = 297-301°C

M.W. = 286.72

I.R. (KBr): 1705; 1635; 1610 cm-1.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 8.90 (d, 2H); 8.70 (m, 2H); 8.50 (s, 2H); 8.28 (d, 1H); 7.89 (dt, 2H).

DESCRIPTION 9

2-(4-pyridyl)quinoline-4-carboxylic acid chloride hydrochloride

1.3 ml (10.4 mmol) of oxalyl chloride were dissolved in 60 ml of CH_2Cl_2. The solution was cooled at -10°C and 3.0 g (14.4 mmol) of 2-(4-pyridyl)quinoline-4-carboxylic acid hydrochloride were added portionwise. The reaction mixture was left 72 hours at room temperature and then evaporated to dryness to yield 4.0 g of the title compound, used without further purification.

$C_{15}H_9ClN_2O \cdot HCl$

M.W. = 305.22

EXAMPLE 1

(R,S)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

1.2 ml (9.4 mmol) of (R,S) α-methylbenzylamine and 1.6 ml (11.7 mmol) of triethylamine (TEA) were dissolved, under nitrogen athmosphere, in 50 ml of a 1:1 mixture of dry CH_2Cl_2 and CH_3CN.

2.0 g (7.8 mmol) of 2-phenylquinoline-4-carbonylchloride, dissolved in 50 ml of a 1:4 mixture of dry CH_2Cl_2 and DMF, were added dropwise to the ice-cooled solution of the amines and the reaction was kept at 0°- 5°C for 1 hour and left at room temperature overnight.

The reaction mixture was evaporated *in-vacuo* to dryness, the residue was dissolved in EtOAc and washed twice with a sat. sol. of $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in-vacuo* to dryness.

The residual oil was crystallized from EtOAc to yield 1.1 g of the title compound as a white solid.

$C_{24}H_{20}N_2O$

M.P. = 156-157°C

M.W. = 352.43

Elemental analysis: Calcd. C,81.79; H,5.72; N,7.95;
Found C,81.99; H,5.69; N,7.89.

I.R. (KBr): 3240;1645 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.29 (d, 1H); 8.32 (d, 2H); 8.13 (d, 1H); 8.13 (s, 1H); 8.06 (d, 1H); 7.81 (ddd, 1H); 7.68-7.52 (m, 4H); 7.47 (d, 2H); 7.39 (dd, 2H); 7.27 (dd, 1H); 5.30 (dq, 1H); 1.52 (d, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 352 (M+.); 337; 232; 204; 77.

EXAMPLE 2

S-(+)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

Prepared as Ex. 1 from 1.2 ml (9.4 mmol) of S-(-)-α-methylbenzylamine, 1.6 ml (11.7 mmol) of TEA, 2.0 g (7.8 mmol) of 2-phenylquinoline-4-carbonylchloride in 100 ml of a mixture of CH_2Cl_2, CH_3CN and DMF.

The work-up of the reaction mixture was carried out in the same manner as described in Ex. 1. The residual oil was crystallized from EtOAc to yield 1.1 g of the title compound.

$C_{24}H_{20}N_2O$

M.P. = 161-162°C

M.W. = 352.43

$[\alpha]_D^{20}$ = + 25 (C = 0.5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.29 (d, 1H); 8.32 (d, 2H); 8.13 (d, 1H); 8.13 (s, 1H); 8.06 (d, 1H); 7.81 (ddd, 1H); 7.68-7.52 (m, 4H); 7.47 (d, 2H); 7.39 (dd, 2H); 7.27 (dd, 1H); 5.30 (dq, 1H); 1.52 (d, 3H).

MS spactra was identical to that of the Ex. 1.

EXAMPLE 3

R-(-)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

Prepared as Ex. 1 from 1.2 ml (9.4 mmol) of R-(+)-α-methylbenzylamine, 1.6 ml (11.7 mmol) of TEA and 2.0 g (7.8 mmol) of 2-phenylquinoline-4-carbonylchloride in 100 ml of a mixture of CH_2Cl_2, CH_3CN and DMF. The work-up of the reaction mixture was carried out in the same manner as described in Ex. 1. The residual oil was crystallized from EtOAc to yield 1.1 g of the title compound.

$C_{24}H_{20}N_2O$

M.P. = 158-160°C

M.W. = 352.43

$[\alpha]_D^{20}$ = - 25 (C = 0.5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

The ^{1}H-NMR and MS spectra were identical to those of the Ex. 1 and Ex. 2.

EXAMPLE 4

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

2.0 g (8.0 mmol) of 2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen athmosphere, in 130 ml of dry THF and 100 ml of CH_3CN.

2.0 g (9.9 mmol) of (D,L) methyl phenylglicinate hydrochloride and 1.5 ml (10.7 mmol) of TEA were added and the reaction mixture was cooled at 5°C.

2.5 g (12.1 mmol) of dicyclohexylcarbodiimide (DCC), dissolved in 10 ml of dry CH_2Cl_2, were added dropwise and the solution was allowed to reach room temperature, stirred for 5 hours and left overnight.

The precipitated dicyclohexylurea was filtered off and the solution was evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and then washed with H_2O.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to obtain 6.0 g of a crude product which was dissolved in 20 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness and the residue flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/ethyl acetate 3:2 containing 0.5% NH_4OH. The crude solid obtained was triturated with warm *i*-Pr_2O, filtered, washed and dried to yield 1.1 g of the title compound.

$C_{25}H_{20}N_2O_3$

M.P. = 170-172°C

M. W. = 396.45

Elemental analysis: Calcd. C,75.74; H,5.09; N,7.07;
Found C,75.88; H,5.12; N,7.06.

I.R. (nujol): 3240; 1750; 1670 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.72 (d, 1H); 8.28 (dd, 2H); 8.20 (dd, 1H); 8.13 (dd, 1H); 8.11 (s, 1H); 7.83 (ddd, 1H); 7.66 (ddd, 1H); 7.60-7.50 (m, 5H); 7.47-7.37 (m, 3H); 5.78 (d, 1H); 3.72 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 396 (M+.); 337; 232; 204.

EXAMPLE 5

(+)-(S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

2.0 g (8.0 mmol) of 2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen athmosphere, in 70 ml of dry THF and 30 ml of CH_3CN.

1.7 g (8.4 mmol) of (L) methyl phenylglicinate hydrochloride, 1.1 ml (9.9 mmol) of N-methylmorpholine and 2.1 g (15.5 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at 0°C.

1.85 g (9.0 mmol) of DCC, dissolved in 10 ml of CH_2Cl_2, were added dropwise and the solution was kept at 0°- 5°C for 1 hour and then at room temperature for 2 hours. The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and sat. sol. NaCl.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 20 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuc* to dryness to obtain 2.6 g of a crude product which was triturated with petroleum ether, filtered, washed with *i*-Pr_2O and then recrystallized from 70 ml of *i*-PrOH to yield 1.7 g of the title compound.

$C_{25}H_{20}N_2O_3$

M.P. = 180-181° C

M.W. = 396.45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$[\alpha]_D^{20}$ = +42.0 (C = 0.5, MeOH).

The ^{1}H-NMR and MS spectra were identical to those of Ex. 4.

EXAMPLE 6

(-)-(R)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

Prepared as Ex. 5 from 2.0 g (8.0 mmol) of 2-phenylquinoline-4-carboxylic acid, 1.7 g (8.4 mmol) of (D) methyl phenylglicinate hydrochloride, 1.1 ml (9.9 mmol) of N-methylmorpholine, 2.1 g (15.5 mmol) of HOBT and 1.85g (9.0 mmol) of DCC in 70 ml of dry THF and 30 ml of CH_3CN.

The work-up of the reaction mixture was carried out in the same manner as described in Ex. 5. The crude product obtained (3.5 g) was triturated twice with warm *i*-Pr_2O, filtered, washed and then recrystallized from 80 ml of *i*-PrOH to yield 2.3 g of the title compound.

$C_{25}H_{20}N_2O_3$

M.P. = 180-181°C

M.W. = 396.45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$[\alpha]_D^{20}$ = -42.0 (C = 0.5, MeOH).

The ^{1}H-NMR and MS spectra were identical to those of Exs. 4 and 5.

EXAMPLE 7

(R,S)-N-[α-(methoxycarbonyl)benzyl]-7-methoxy-2-phenylquinoline-4-carboxamide

1.0 g (5.0 mmol) of (D,L) methyl phenylglicinate hydrochloride were dissolved, under nitrogen athmosphere, in 30 ml of dry DMF.

2.5 g (18.1 mmol) of anhydrous potassium carbonate were added and the solution cooled at 0°C.

0.7 g (2.3 mmol) of the compound of Description 3, dissolved in 25 ml of dry DMF, were added dropwise and the solution was kept at 0°- 5°C for 1 hour and at room temperature overnight.

The reaction mixture was evaporated *in-vacuo* to dryness and the residue was dissolved in EtOAc and washed twice with H_2O. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in-vacuo* to dryness.

The residual oil was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/ethyl acetate 3:2 containing 0.5% NH_4OH to afford 0.1 g of the crude product which was triturated with *i*-Pr_2O to yield 0.08 g of the title compound.

$C_{26}H_{22}N_2O_4$

M.P. = 187-190°C

M.W. = 426.48

I.R. (KBr): 3220; 1750; 1660; 1620 cm^{-1}.

300 MHz ^{1}H-NMR ($CDCl_3$): δ : 8.13-8.08 (m, 3H); 7.80 (s, 1H); 7.55-7.38 (m, 9H); 7.21 (dd, 1H); 7.02 (d broad, H); 5.88 (d, 1H); 3.97 (s,3H); 3.80 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 426 (M+.); 367 ; 262 ; 234; 191;77.

EXAMPLE 8

(R,S)-N-[α-(methoxycarbonyl)benzyl]-7-hydroxy-2-phenylquinoline-4-carboxamide

Prepared as Ex. 5 from 2.1 g (5.3 mmol) of the compound of Description 4, 1.08 g (5.3 mmol) of (D,L) methyl phenylglicinate hydrochloride, 1.5 ml (10.7 mmol) of TEA, 1.7 g (12.5 mmol) of HOBT and 1.2 g (5.8 mmol) of DCC in 70 ml of dry THF and 30 ml of CH_3CN.

The work-up of the reaction mixture was carried out in the same manner as described

in Ex. 5. The crude product obtained was triturated with *i*-Pr_2O and then recrystallized twice from *i*-PrOH to yield 0.06 g of the title compound.

$C_{25}H_{20}N_2O_4$

M.P. = 256-257°C

M.W. = 412.45

I.R. (KBr): 3270; 1750; 1650; 1620 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 10.30 (s broad, 1H); 9.64 (d, 1H); 8.22 (d, 2H); 8.04 (d, 1H); 7.85 (s, 1H); 7.60-7.34 (m, 9H); 7.21 (dd, 1H); 5.74 (d, 1H); 3.71 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 412 (M+.); 353; 248; 220; 77.

EXAMPLE 9

(R,S)-N-[α-(carboxy)benzyl]-7-methoxy-2-phenylquinoline-4-carboxamide hydrochloride

0.18 g (0.4 mmol) of the product of Ex. 7 were dissolved in 10 ml of 10% HCl and 5 ml of dioxane. The reaction mixture was refluxed and stirred for 3 hours, then evaporated *in-vacuo* to dryness.

The crude product was triturated with warm EtOAc (containing a few drops of EtOH) to yield 0.16 g of the title compound.

$C_{25}H_{20}N_2O_4$.HCl

M.P. = 228-230°C

M.W. = 448.91

I.R. (KBr): 3180; 1735; 1655; 1630 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.6 (d, 1H); 8.26 (dd, 2H); 8.14 (d, 1H); 7.98 (s, 1H); 7.63-7.52 (m, 6H); 7.46-7.36 (m, 3H); 7.33 (dd, 1H); 5.66 (d, 1H); 3.98 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 412 (M+.); 368 ; 262; 234; 191; 77.

EXAMPLE 10

(R,S)-N-[α-(methylaminocarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

0.45 g (1.1 mmol) of the product of Ex. 4 were dissolved in 40 ml of 33% $MeNH_2$/EtOH; a catalitic amount of NaCN was added and the reaction mixture was heated at 70°C for 1 hour in a parr apparatus. The internal pressure rised to 40 psi. The solution was evaporated *in-vacuo* to dryness and the residue was triturated with water, filtered, dried and recrystallized from a mixture of *i*-PrOH (50 ml) and EtOH (30 ml) to yield 0.2 g of the title compound.

$C_{25}H_{21}N_3O_2$
M.P. = 261-263°C
M.W. = 395.47
Elemental analysis: Calcd. C,75.93; H,5.35; N,10.63;
Found C,75.65; H,5.34; N,10.55.
I.R. (KBr): 3300; 3270; 1660; 1635 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.48 (d, 1H); 8.33-8.25 (m, 3H); 8.18-8.10 (m, 3H); 7.80 (ddd, 1H); 7.68-7.50 (m, 6H); 7.40-7.28 (m, 3H); 5.75 (d, 1H); 2.63 (d,3H).
MS (EI; source 200 °C; 70 V; 200 mA): 395 (M+.); 337; 232; 204; 77.

EXAMPLE 11

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-thienyl)quinoline-4-carboxamide

Prepared as Ex. 5 from 2.0 g (7.3 mmol) of 2-(2-thienyl)quinoline-4-carboxylic acid, 1.7 g (8.4 mmol) of (D,L) methyl phenylglicinate hydrochloride, 1.1 ml (10 mmol) of N-methylmorpholine, 2.1 g (15.5 mmol) of HOBT and 1.85 g (9.0 mmol) of DCC in 70 ml of dry THF, 30 ml of CH_3CN and 10 ml of CH_2Cl_2.
The work-up of the reaction mixture was carried out in the same manner as described in Ex. 5. The crude product obtained was crystallized from EtOAc and then recrystallized from abs. EtOH to yield 0.9 g of the title compound.
$C_{23}H_{18}N_2O_3S$
M.P. = 178-180°C
M.W. = 402.47
Elemental analysis: Calcd. C,68.64; H,4.51; N,6.96;
Found C,67.50; H,4.99; N,7.43.
I.R. (KBr): 3300; 1745; 1645 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.70 (d, 1H); 8.12 (d, 1H); 8.08 (s, 1H); 8.04 (d, 1H); 8.02 (d, 1H); 7.19 (t, 1H); 7.76 (d, 1H); 7.62 (t, 1H); 7.53 (d, 2H); 7.46-7.37 (m, 3H); 7.3 (dd, 1H); 5.68 (d, 1H); 3.68 (s, 3H).
MS (EI; source 200 °C; 70 V; 200 mA): 402 (M+.); 343; 238; 210; 77.

EXAMPLE 12

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-furyl)quinoline-4-carboxamide

Prepared as Ex. 1 from 7.2 g (35.5 mmol) of (D,L) methyl phenylglicinate hydrochloride, 12.4 ml (88.8 mmol) of TEA and 9.1 g (35.5 mmol) of crude 2-(2-

furyl)quinoline-4-carbonylchloride in 350 ml of a mixture of CH_2Cl_2, CH_3CN and DMF. The work-up of the reaction mixture was carried out in the same manner as described in Ex. 1. The crude product obtained was triturated with MeOH to yield 3.3 g of the title compound.

$C_{23}H_{18}N_2O_4$

M.P. = 178-180°C

M.W. = 386.405

Elemental analysis: Calcd. C,71.49; H,4.70; N,7.25;
Found C,71.67; H,4.74; N,7.17.

I.R. (KBr): 3300; 1750; 1650 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.72 (d, 1H); 8,12 (d, 1H); 8.06 (d, 1H); 7.96 (dd, 1H); 7.92 (s, 1H); 7.80 (ddd, 1H); 7.62 (ddd, 1H); 7.52 (dd, 2H); 7.45-7.35 (m, 4H); 6.73 (dd, 1H); 5.77 (d, 1H); 3.74 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 386 (M+.); 327; 222; 194; 77.

EXAMPLE 13

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-pyridyl)quinoline-4-carboxamide

Prepared as Ex. 1 from 3.4 g (16.7 mmol) of (D,L) methyl phenylglicinate hydrochloride, 3.9 ml (27.8 mmol) of TEA and 3.0 g (11.1 mmol) of 2-(4-pyridyl)quinoline-4-carbonylchloride in 100 ml of a mixture of CH_2Cl_2, CH_3CN and DMF. The work-up of the reaction mixture was carried out in the same manner as described in Ex. 1. The crude product obtained was recrystallized three times from EtOAc to yield 1.9 g of the title compound.

$C_{24}H_{19}N_3O_3$

M.P. = 172-174°C

M.W. = 397.43

Elemental analysis: Calcd. C,72.53; H,4.82; N,10.57;
Found C,71.87; H,4.87; N,10.44.

I.R. (KBr): 3240; 1750; 1670 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.74 (d, 1H); 8.79 (dd, 2H); 8.27-8.17 (m, 5H); 7.89 (ddd, 1H); 7.74 (ddd, 1H); 7.54 (dd, 2H); 7.47-7.38 (m, 3H); 5.8 (d, 1H); 3.75 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 397 (M+.); 338; 233; 205; 77.

EXAMPLE 14

(R,S)-N-[α-(methoxycarbonyl)-2-thienylmethyl]-2-phenylquinoline-4-

carboxamide

Prepared as Ex. 1 from 1.94 g (9.4 mmol) of (D,L) methyl thienylglicinate hydrochloride, 2.7 ml (19.5 mmol) of TEA and 2.0 g (7.8 mmol) of 2-phenylquinoline-4-carbonylchloride in 100 ml of a mixture of CH_2Cl_2, CH_3CN and DMF. The work-up of the reaction mixture was carried out in the same manner as described in Ex. 1. The crude product obtained was recrystallized three times from EtOAc to yield 0.66 g of the title compound.

$C_{23}H_{18}N_2O_3S$

M.P. = 144-145°C

M.W. = 402.47

Elemental analysis: Calcd. C,68.64; H,4.51; N,6.96;
Found C,68.81; H,4.46; N,6.96.

I.R. (KBr): 3295; 1745; 1640 cm^{-1}.

300 MHz ^{1}H-NMR ($CDCl_3$): δ 8.25 (dd, 1H); 8.22 (dd, 1H); 8.17 (dd, 2H); 7.95 (s, 1H); 7.78 (ddd, 1H); 7.60 (ddd, 1H); 7.56-7.45 (m, 3H); 7.35 (dd,1H) ; 7.20 (d, 1H); 7.05 (dd, 1H); 7.05 (s broad, 1H); 6.22 (d, 1H); 3.9 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 402 (M+.); 343; 232; 204.

EXAMPLE 15

(R,S)-N-[α-(methoxycarbonylmethyl)benzyl]-2-phenylquinoline-4-carboxamide

Prepared as Ex. 5 from 1.39 g (5.60 mmol) of 2-phenylquinoline-4-carboxylic acid, 1.2 g (5.60 mmol) of (R,S) methyl 3-amino-3-phenylpropionate hydrochloride, 0.78 ml (5.60 mmol) of TEA, 1.51 g (11.2 mmol) of HOBT and 2.31 g (11.2 mmol) of DCC in 10 ml of dry THF, 4 ml of CH_3CN and 7 ml of CH_2Cl_2. The work-up of the reaction mixture was carried out in the same manner as described in Ex. 5. The crude product obtained was dissolved in CH_2Cl_2 and left at 0°C overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness to obtain 1.4 g of a crude product which was triturated with a mixture of *i*-Pr_2O/acetone 99:1 to yield 1.2 g of the title compound as a white solid.

$C_{26}H_{22}N_2O_3$

M.P. = 156-158°C

M.W. = 410.47

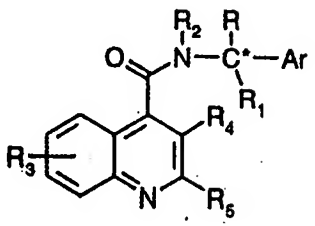
Elemental analysis: Calcd. C,76.07; H,5.40; N,6.82;
Found C,75.77; H,5.38; N,6.94.

I.R. (KBr): 3295; 1755; 1645; 1590; 1530 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.40 (d, 1H); 8.29 (dd, 2H); 8.14 (d, 1H); 8.07 (d, 1H); 8.04 (s, 1H); 7.83 (ddd, 1H); 7.66-7.52 (m, 4H); 7.50 (d, 2H); 7.40 (dd, 2H); 7.31 (ddd, 1H); 5.60 (dt, 1H); 3.65 (s, 3H); 3.04-2.89 (m, 2H).

MS (EI; source 200 °C; 70 V; 200 mA): 410 (M+.); 337; 233; 205.

TABLE 1



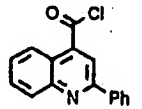
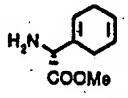
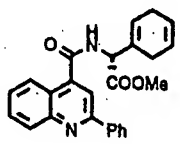
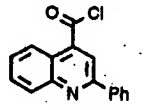
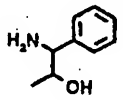
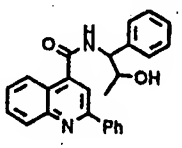
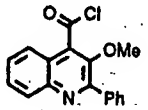
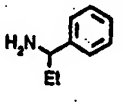
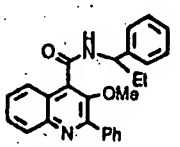
Ex.	Ar	R	R_1	R_2	R_3	R_4	R_5	*	Molecular formula	Melting point °C	$[\alpha]_D^{20}$ c=0.5,MeOH
1	Ph	Me	H	H	H	H	Ph	(R,S)	$C_{24}H_{20}N_2O$	156-157	
2	Ph	Me	H	H	H	H	Ph	(S)	$C_{24}H_{20}N_2O$	161-162	+25° [a]
3	Ph	Me	H	H	H	H	Ph	(R)	$C_{24}H_{20}N_2O$	158-160	-25° [a]
4	Ph	COOMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{20}N_2O_3$	170-172	
5	Ph	COOMe	H	H	H	H	Ph	(S)	$C_{25}H_{20}N_2O_3$	180-181	+42°
6	Ph	COOMe	H	H	H	H	Ph	(R)	$C_{25}H_{20}N_2O_3$	180-181	-42°
7	Ph	COOMe	H	H	7-OMe	H	Ph	(R,S)	$C_{26}H_{22}N_2O_4$	187-190	
8	Ph	COOMe	H	H	7-OH	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4$	256-257	
9	Ph	COOH	H	H	7-OMe	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4$.HCl	228-230	
10	Ph	CONHMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{21}N_3O_2$	261-263	
11	Ph	COOMe	H	H	H	H	2-thienyl	(R,S)	$C_{23}H_{18}N_2O_3S$	178-180	
12	Ph	COOMe	H	H	H	H	2-furyl	(R,S)	$C_{23}H_{18}N_2O_4$	178-180	
13	Ph	COOMe	H	H	H	H	4-Py	(R,S)	$C_{24}H_{19}N_3O_3$	172-174	
14	2-thienyl	COOMe	H	H	H	H	Ph	(R,S)	$C_{23}H_{18}N_2O_3S$	144-145	
15	Ph	CH_2COOMe	H	H	H	H	Ph	(R,S)	$C_{26}H_{22}N_2O_3$	156-158	

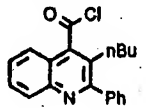
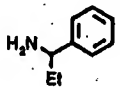
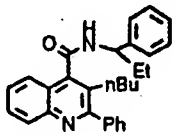
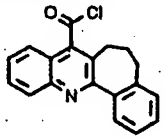
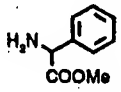
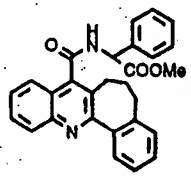
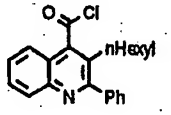
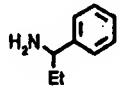
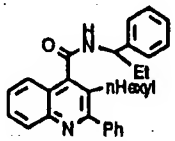
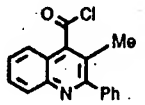
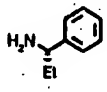
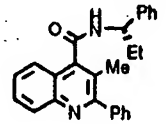
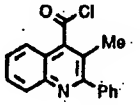
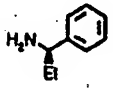
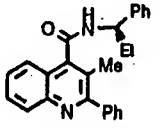
[a] solvent DMF

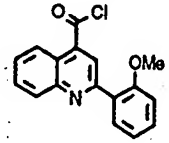
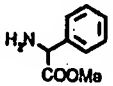
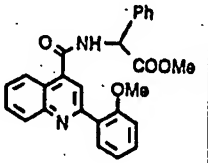
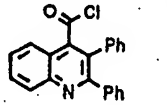
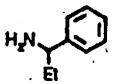
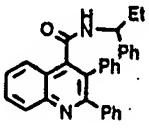
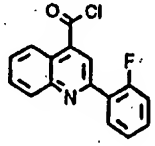
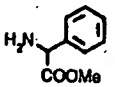
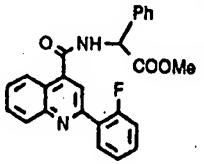
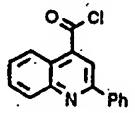
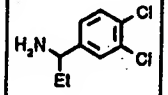
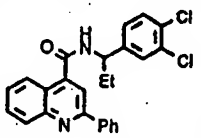
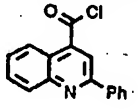
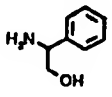
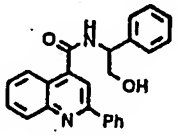
The compounds of the Examples 16-49 of general formula (I) (grouped in the following Table 2) were synthesized starting from the appropriate acyl chlorides of (II) and amines of formula (III) shown in the table and following the synthetic procedure described in Example 1. Acyl chlorides were synthesized starting from the corresponding acid of formula (II) and following Description 1. Reaction yields are calculated on the purified, but unrecrystallized material. Analytical and spectroscopic data of the compounds of the Examples 16-49 are grouped in Table 5.

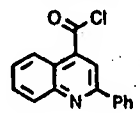
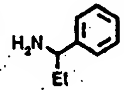
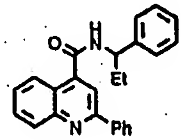
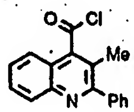
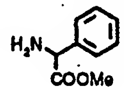
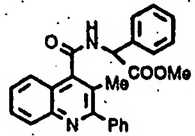
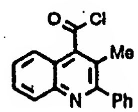
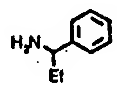
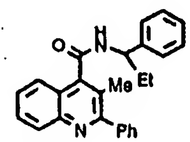
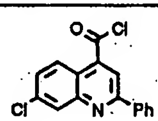
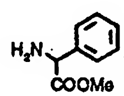
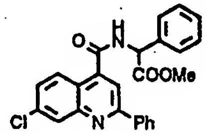
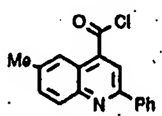
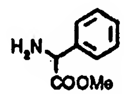
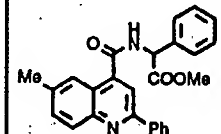
Table 2

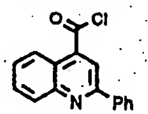
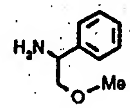
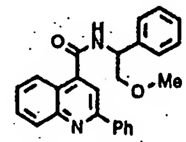
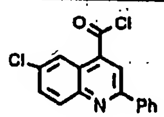
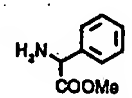
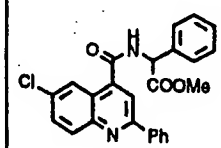
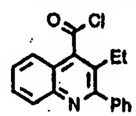
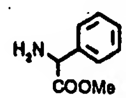
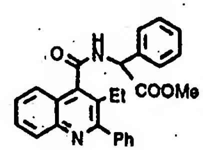
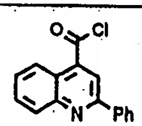
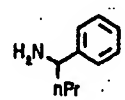
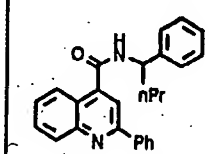
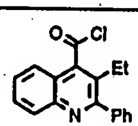
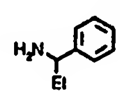
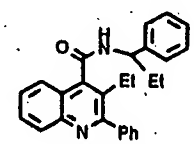
Acyl chloride of (II) + (III) ⟶ (I)

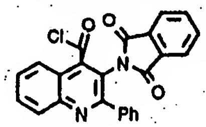
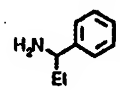
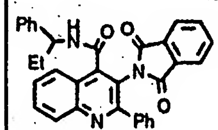
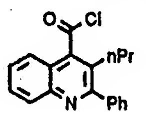
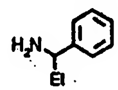
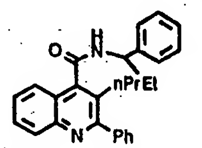
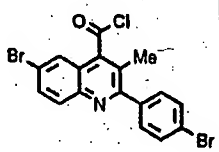
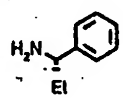
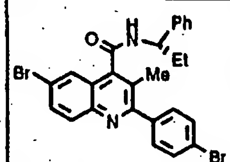
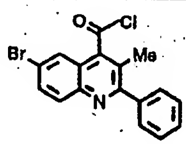
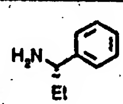
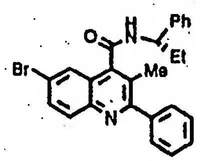
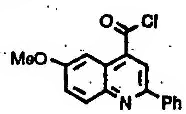
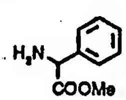
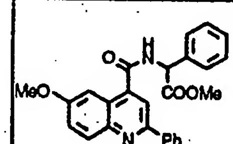
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
16				(R)	$C_{25}H_{22}N_2O_3$	398.47	16	120-122 (iPr_2O)	- 18.9 (c=0.5)
17				(R,S) single diast.	$C_{25}H_{22}N_2O_2$	382.47	44	204-205 (iPrOH/ iPr_2O)	
18				(R,S)	$C_{26}H_{24}N_2O_2$	396.49	48	163-165 (iPrOH/ iPr_2O)	

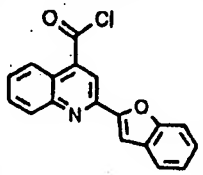
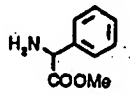
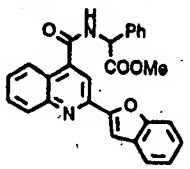
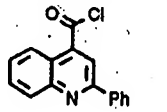
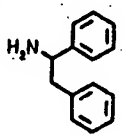
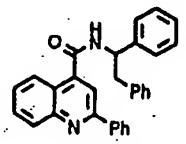
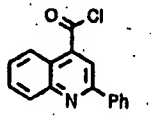
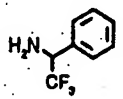
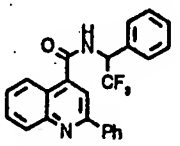
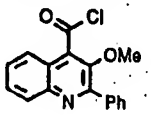
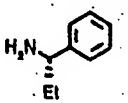
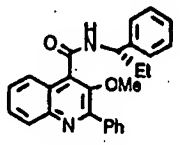
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
19				(R,S)	$C_{29}H_{30}N_2O$	422.58	30	147-150 (hexane)	
20				(R,S)	$C_{28}H_{24}N_2O_3$	436.52	43	186-188 (iPrOH/ iPr_2O)	
21				(R,S)	$C_{31}H_{34}N_2O$	450.63	24	131-134 (hexane/ iPr_2O)	
22				(S)	$C_{26}H_{24}N_2O$	380.49	58	153-155 (iPr_2O)	- 36.0
23				(R)	$C_{26}H_{24}N_2O$	380.49	78	155-156 (iPr_2O)	+ 35.9

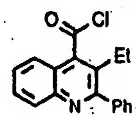
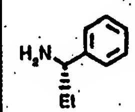
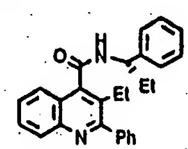
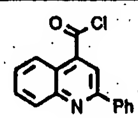
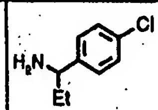
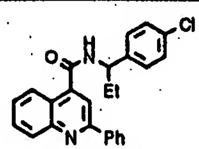
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
24				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	55	124-125 (toluene)	
25				(R,S)	$C_{31}H_{26}N_2O$	442.57	49	198-200 (toluene)	
26				(R,S)	$C_{25}H_{19}FN_2O_3$	414.44	75	146-147 (toluene)	
27				(R,S)	$C_{25}H_{20}Cl_2N_2O$	435.36	44	193-194 (toluene)	
28				(R,S)	$C_{24}H_{20}N_2O_2$	368.43	24	117-119 (toluene)	

Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
29				(R,S)	$C_{25}H_{22}N_2O$	366.47	80	141-143 (toluene)	
30				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	60	180-181 (toluene / iPr_2O)	
31				(R,S)	$C_{26}H_{24}N_2O$	380.49	55	156-158 (toluene/ hexane)	
32				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	48	180-183 (toluene)	
33				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	48	179-181 (toluene)	

Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
34				(R,S)	$C_{25}H_{22}N_2O_2$	382.47	42	144-145 (toluene)	
35				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	46	197-199 (toluene)	
36				(R,S)	$C_{27}H_{24}N_2O_3$	424.50	52	156-157 (toluene/ hexane)	
37				(R,S)	$C_{26}H_{24}N_2O$	380.49	50	149-150 (toluene)	
38				(R,S)	$C_{27}H_{26}N_2O$	394.52	53	158-159 (Et_2O/ iPr_2O)	

Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
39				(R,S)	$C_{33}H_{25}N_3O_3$	511.58	16	201-202 (toluene)	
40				(R,S)	$C_{28}H_{28}N_2O$	408.55	71	149-151 (toluene/ hexane)	
41				(S)	$C_{26}H_{22}Br_2N_2O$	538.30	24	230-231 (Et_2O / iPr_2O)	- 49.8 (c=0.2)
42				(S)	$C_{26}H_{23}BrN_2O$	459.40	39	179-180 (hexane/ iPrOH)	- 60.5
43				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	45	209-211 (Me_2CO)	

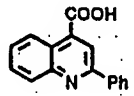
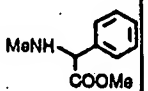
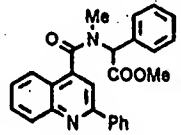
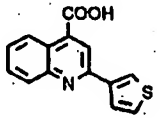
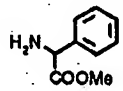
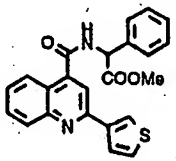
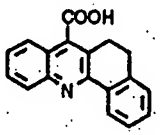
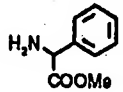
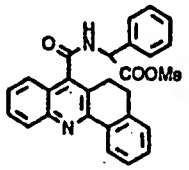
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
44				(R,S)	$C_{27}H_{20}N_2O_4$	436.47	65	240-241 (EtOAc)	
45				(R,S)	$C_{30}H_{24}N_2O$	428.53	47	194-196 (EtOAc)	
46				(R,S)	$C_{24}H_{17}F_3N_2O$	406.41	45	180-181 (toluene)	
47				(S)	$C_{26}H_{24}N_2O_2$	396.49	58	132-134 (Me_2CO)	- 45 (c=0.5)

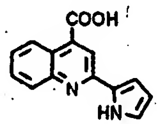
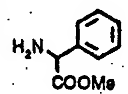
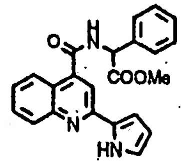
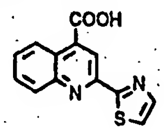
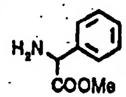
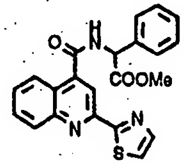
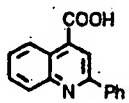
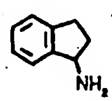
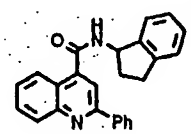
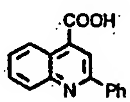
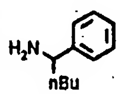
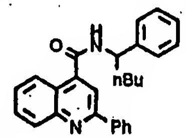
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
48				(S)	$C_{27}H_{26}N_2O$	394.52	53	118-120 (hexane)	- 42 (c=0.5)
49				(R,S)	$C_{25}H_{21}ClN_2O$	400.91	40	177-178 (toluene)	

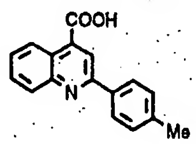
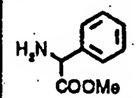
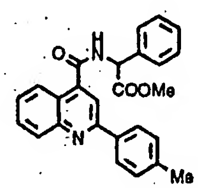
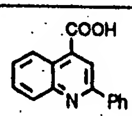
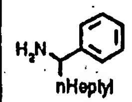
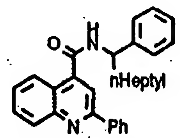
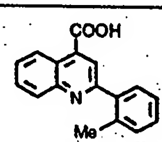
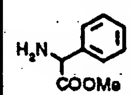
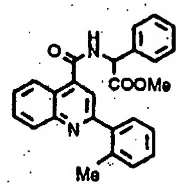
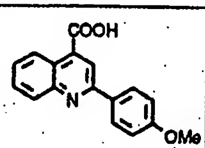
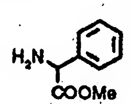
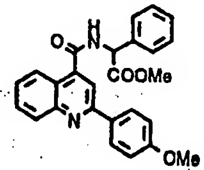
The compounds of the Examples 50-88 of general formula (I) (grouped in the following Table 3) were synthesized starting from the appropriate reagents (II) and (III) shown in the table and following the synthetic procedure described in Example 5. Reaction yields are calculated on the purified, but unrecrystallized material. Analytical and spectroscopic data of the compounds of the Examples 50-88 are grouped in Table 5.

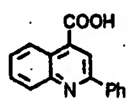
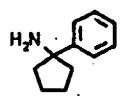
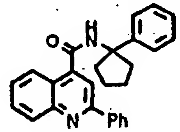
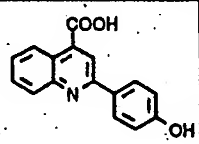
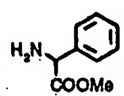
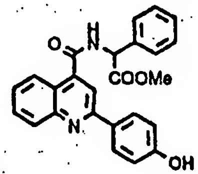
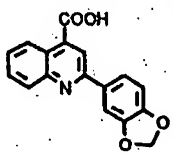
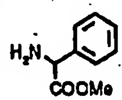
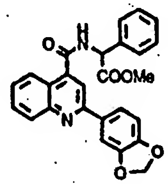
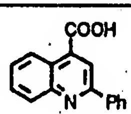
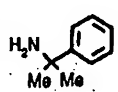
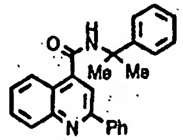
Table 3

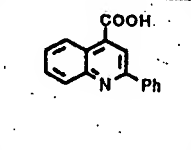
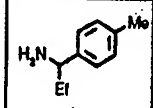
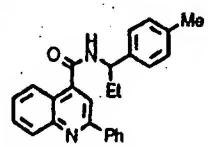
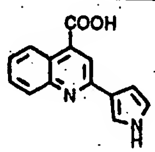
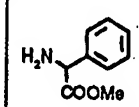
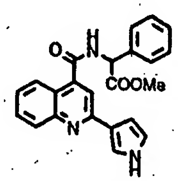
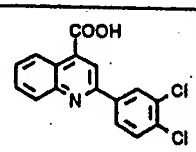
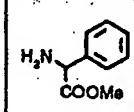
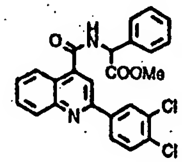
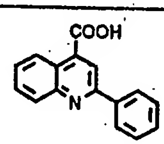
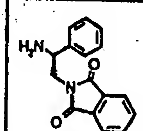
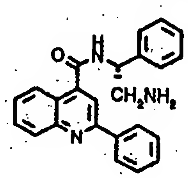
(II) + (III) ⟶ (I)

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
50				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	46	128-129 (iPrOH)	
51				(R,S)	$C_{23}H_{18}N_2O_3S$	402.47	88	169-171 (iPrOH)	
52				(R,S)	$C_{27}H_{22}N_2O_3$	422.49	41	217-219 (EtOH abs.)	

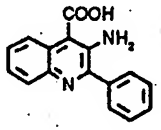
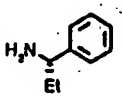
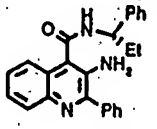
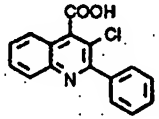
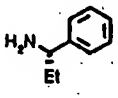
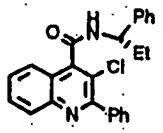
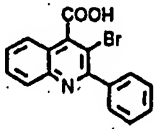
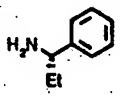
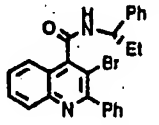
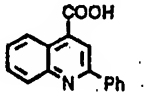
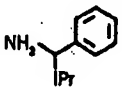
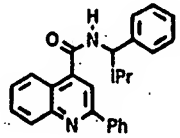
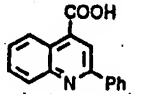
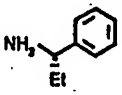
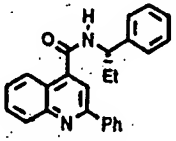
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
53				(R,S)	$C_{23}H_{19}N_3O_3$	385.42	44	181-182 (iPrOH)	
54				(R,S)	$C_{22}H_{17}N_3O_3S$	403.45	50	209-211 (iPrOH)	
55				(R,S)	$C_{25}H_{20}N_2O$	364.45	95	183-184 (iPrOH)	
56				(R,S)	$C_{27}H_{26}N_2O$	394.52	77	155-156 (iPrOH/ iPr_2O)	

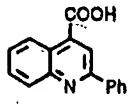
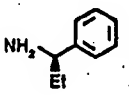
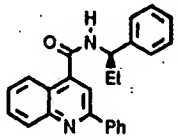
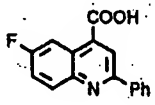
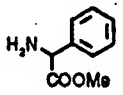
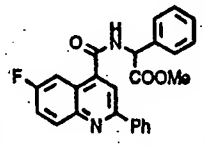
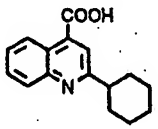
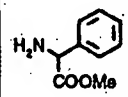
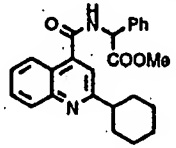
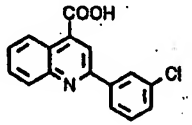
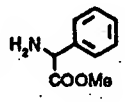
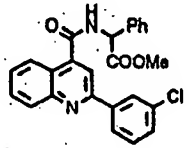
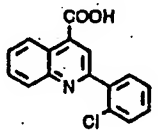
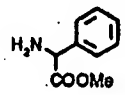
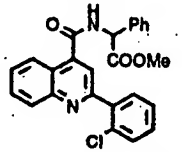
Ex.	(II)	(III)	(I)	Stereo chemistr y	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
57				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	83	172-174 (iPrOH)	
58				(R,S)	$C_{30}H_{32}N_2O$	436.60	91	121-128 (iPr_2O)	
59				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	79	180-182 (iPrOH)	
60				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	62	182-183 (iPrOH)	

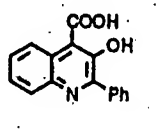
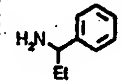
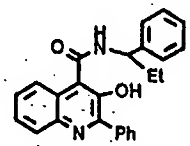
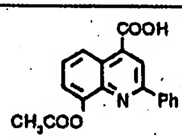
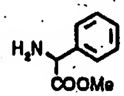
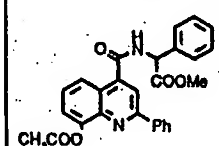
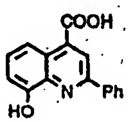
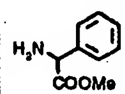
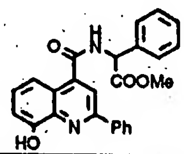
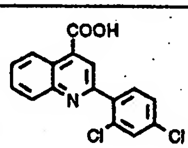
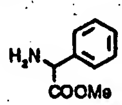
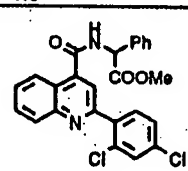
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
61				--	$C_{27}H_{24}N_2O$	392.51	82	164-165 (iPrOH)	
62				(R,S)	$C_{25}H_{20}N_2O_4$	412.45	50	226-227 (iPrOH)	
63				(R,S)	$C_{26}H_{20}N_2O_5$	440.46	70	186-187 (iPrOH)	
64				--	$C_{25}H_{22}N_2O$	366.47	75	173-174 (iPrOH)	

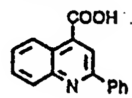
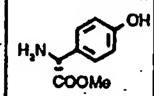
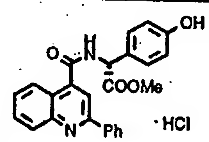
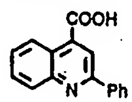
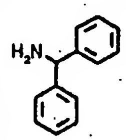
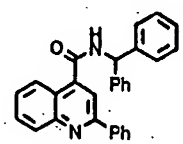
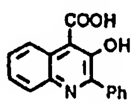
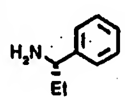
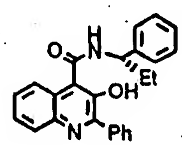
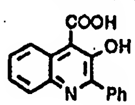
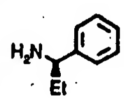
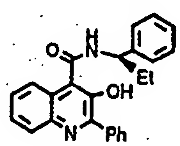
• Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
65				(R,S)	$C_{26}H_{24}N_2O$	380.49	90	160-162 (iPrOH)	
66				(R,S)	$C_{23}H_{19}N_3O_3$	385.42	10	202-204 (iPr_2O)	
67				(R,S)	$C_{25}H_{18}Cl_2N_2O_3$	465.34	59	164-165 (iPrOH)	
68			 (a)	(R)	$C_{24}H_{21}N_3O$	367.45	49	139-141 (iPrOH/ iPr_2O)	- 6.9 (c=0.5)

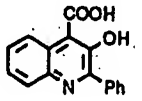
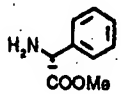
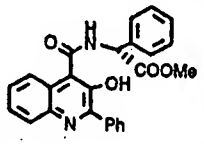
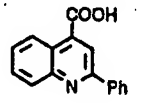
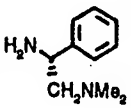
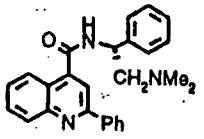
(a) the phthalimido protecting group was removed by refluxing for 4h with hydrate hydrazine in 95% EtOH/1,2 dichloroethane, 9:1 respectively and then adding 37% HCl (up to pH=1) and refluxing an additional hour.

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
69				(S)	$C_{25}H_{23}N_3O$	381.48	78	153-155 (iPrOH/ iPr_2O)	- 68.0 (c=0.5)
70				(S)	$C_{25}H_{21}ClN_2O$	400.91	58	137-139 (toluene/ hexane)	- 40.5 (c=0.5)
71				(S)	$C_{25}H_{21}BrN_2O$	445.37	20	119-122 (toluene/ hexane)	- 41.4 (c=0.5)
72				(R,S)	$C_{26}H_{24}N_2O$	380.49	59	165-166 (iPrOH)	
73				(S)	$C_{25}H_{22}N_2O$	366.46	77	140-141 (iPrOH)	- 26.7

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
74				(R)	$C_{25}H_{22}N_2O$	366.46	51	151-152 (iPrOH)	+ 26.6
75				(R,S)	$C_{25}H_{19}FN_2O_3$	414.44	44	174-176 (toluene/ EtOAc)	
76				(R,S)	$C_{25}H_{26}N_2O_3$	402.50	53	151-153 (EtOAc)	
77				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	68	161-163 (toluene/ hexane)	
78				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	43	175-178 (toluene/ hexane)	

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
79				(R,S)	$C_{25}H_{22}N_2O_2$	382.47	47	168-169 (toluene)	
80				(R,S)	$C_{27}H_{22}N_2O_5$	454.49	16	193-194 (toluene)	
81				(R,S)	$C_{25}H_{20}N_2O_4$	412.40	32	178-180 (toluene)	
82				(R,S)	$C_{25}H_{18}Cl_2N_2O_3$	465.34	61	142-143 (iPrOH)	

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
83				(R)	$C_{25}H_{20}N_2O_4$ ·HCl	448.88	50	140 dec. (Me$_2$CO)	- 7
84				--	$C_{29}H_{22}N_2O$	414.51	42	182-184 (EtOAc)	
85				(S)	$C_{25}H_{22}N_2O_2$	382.47	66	122-125 (iPr$_2$O)	- 28.4 (c=0.5)
86				(R)	$C_{25}H_{22}N_2O_2$	382.47	66	122-125 (hexane/ EtOAc)	+ 27.2 (c=0.5)

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
87				(R)	$C_{25}H_{20}N_2O_4$	412.45	70	125-127 (iPr$_2$O)	- 50 (c=0.5)
88				(R)	$C_{26}H_{25}N_3O$	395.51	26	133-135 (iPr$_2$O/ iPrOH)	- 11.2 (c=0.5)

The compounds of the Examples 89-92 of general formula (I) (grouped in the following Table 4) were synthesized starting from other compounds of formula (I) (i.e. compounds of formula Ic) and following the synthetic procedures described in Example 10 (for compounds of the Examples 89, 90 and 91) and in Example 9 (for compound of the Example 92). Reaction yields are calculated on the purified, but unrecrystallized material. Analytical and spectroscopic data of the compounds of the Examples 89-92 are grouped in Table 5.

Table 4

(Ic) ⟶ (I)

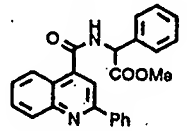
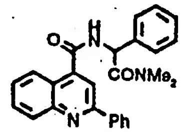
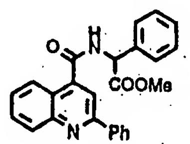
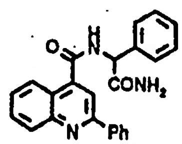
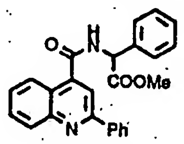
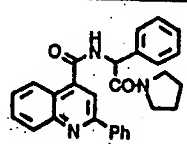
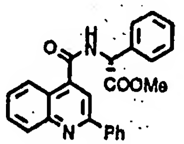
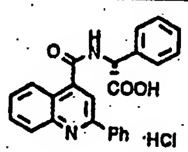
Ex.	(Ic)	(I)	Stereo chemistry	Molecular formula	M.W.	yield (%)	m.p. (°C) (recryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
89			(R,S)	$C_{26}H_{23}N_3O_2$	409.49	22	219-221 (iPrOH /EtOH)	
90			(R,S)	$C_{24}H_{19}N_3O_2$	381.43	95	237-238 (iPrOH /EtOH)	
91			(R,S)	$C_{28}H_{25}N_3O_2$	435.53	69	199-200 (iPrOH)	
92			(R)	$C_{24}H_{18}N_2O_3$ ·HCl	418.88	94	203-205 (acetone)	- 40.0 (c=0.5)

Table 5. Analytical and spectroscopic data of compounds of Examples 16-92

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
16		3240; 1750; 1640; 1595; 1545	398 (M+.); 232; 204	9.40 (d,1H); 8.30 (d,2H); 8.18 (d,1H); 8.13 (d,1H); 8.10 (s,1H); 7.83 (dd,1H); 7.66 (dd,1H); 7.63-7.51 (m,3H); 5.87 (s br,1H); 5.70 (m,2H); 5.12 (d,1H); 3.80 (s,3H); 2.92-2.60 (m,4H).
17	Calcd. C,78.51; H,5.80; N,7.32 Found C,78.27; H,5.83; N,7.24	3400; 3200; 1640; 1595; 1532	337 $(M-C_2H_4OH)+$; 232; 204	9.20 (d,1H); 8.31 (d,2H); 8.14 (d,1H); 8.08 (s,1H); 8.04 (d,1H); 7.82 (dd,1H); 7.64-7.51 (m,4H); 7.47 (d,2H); 7.37 (dd,2H); 7.27 (dd,1H); 5.10 (dd,1H); 4.81 (d,1H); 4.13 (dq,1H); 1.18 (d,3H).
18	Calcd. C,78.76; H,6.10; N,7.07 Found C,78.60; H,6.08; N,7.00	3260; 3220; 1632; 1550 *	396 (M+.); 367; 262; 219	9.24 (d,1H); 8.07 (d,1H); 7.97 (dd,2H); 7.76-7.70 (m,1H); 7.62-7.51 (m,5H); 7.46 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.10 (dt,1H); 3.52 (s,3H); 1.82 (dq,2H); 1.00 (t,3H).
19	Calcd. C,82.43; H,7.16; N,6.63 Found C,82.31; H,7.20; N,6.58	3240; 1630; 1540	423 (MH+) •	(353 K): 8.89 (d br,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.60-7.42 (m,9H); 7.36 (dd,2H); 7.28 (dd,1H); 5.13 (dt,1H); 2.66 (m,2H); 1.90 (ddq,2H); 1.30 (m,2H); 1.00 (t,3H); 0.95 (m,2H); 0.57 (t br,3H).
20	Calcd. C,77.04; H,5.54; N,6.42 Found C,76.81; H,5.54; N,6.35	3290; 1760; 1645; 1590; 1532	436 (M+.); 377; 272; 271	(353 K): 9.50 (d,1H); 8.08 (d,1H); 7.88 (d,1H); 7.80-7.72 (m,2H); 7.60 (dd,1H); 7.52 (dd,2H); 7.47-7.30 (m,6H); 5.90 (d,1H); 2.60 (t,2H); 2.57 (t,2H); 2.26-2.06 (m,2H).

Ex.	Elemental analysis	IR (KBr); cm-1	MS (EI; source 200°C; 70 eV; 200 µA)	300 MHz ^{1}H NMR (DMSO), 303 K
21	Calcd. C,82.63; H,7.61; N,6.22 Found C,82.84; H,7.64; N,6.16	3270; 1635; 1550 *	450 (M+.); 421; 316	(373 K): 8.71 (d br,1H); 7.99 (d,1H); 7.70 (m,2H); 7.52-7.42 (m,8H); 7.37 (dd,2H); 7.27 (dd,1H); 5.12 (dt,1H); 2.67 (dd,2H); 1.91 (ddq,2H); 1.36-1.26 (m,2H); 1.12-1.02 (m,2H); 1.00 (t,3H); 1.00-0.90 (m,4H); 0.76 (t,3H).
22	Calcd. C,82.07; H,6.36; N,7.36 Found C,81.95; H,6.33; N,7.30	3260; 1630; 1535	380 (M+.); 351; 246; 218	(353 K): 8.90 (d br,1H); 8.01 (d,1H); 7.72 (dd,1H); 7.65 (d br,1H); 7.60-7.49 (m,6H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.12 (dt,1H); 2.30 (s,3H); 1.98-1.78 (m,2H); 0.99 (t,3H).
23	Calcd. C,82.07; H,6.36; N,7.36 Found C,81.80; H,6.37; N,7.30	3260; 1630; 1535	380 (M+.); 351; 246; 218	(353 K): 8.90 (d br,1H); 8.01 (d,1H); 7.72 (dd,1H); 7.65 (d br,1H); 7.60-7.49 (m,6H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.12 (dt,1H); 2.30 (s,3H); 1.98-1.78 (m,2H); 0.99 (t,3H).
24	Calcd. C,73.22; H,5.20; N,6.57 Found C,72.88; H,5.25; N,6.44	3282; 1750; 1640; 1530	426 (M+.); 367; 277	9.65 (d,1H); 8.18 (d,1H); 8.11 (d,1H); 7.96 (s,1H); 7.83 (dd,1H); 7.81 (dd,1H); 7.66 (dd,1H); 7.54-7.46 (m,3H); 7.44-7.33 (m,3H); 7.22 (d,1H); 7.13 (dd,1H); 5.80 (d,1H); 3.87 (s,1H); 3.71 (s,3H).
25	Calcd. C,84.13; H,5.92; N,6.33 Found C,82.28; H,5.86; N,6.19	3250; 1630; 1545	442 (M+.); 413; 308; 280	8.86 (d,1H); 8.13 (d,1H); 7.83 (dd,1H); 7.71-7.59 (m,2H); 7.31-7.14 (m,12H); 7.04 (d br,2H); 4.75 (dt,1H); 1.58-1.42 (m,2H); 0.63 (t br,3H).
26	Calcd. C,72.45; H,4.62; N,6.76 Found C,72.19; H,4.66; N,6.69	3320; 1745; 1650; 1595	414 (M+.); 355; 250; 222	9.70 (d,1H); 8.21 (d,1H); 8.16 (d,1H); 8.07 (dd,1H); 7.90 (d,1H); 7.86 (dd,1H); 7.72 (dd,1H); 7.64-7.55 (m,1H); 7.51 (dd,1H); 7.45-7.34 (m,4H); 5.80 (d,1H); 3,75 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
27	Calcd. C,69.03; H,4.62; N,6.44 Found C,68.97; H,4.63; N,6.43	3250; 1650; 1585; 1550	434 (M+.); 405; 232; 204	9.50 (d,1H); 8.31 (d,2H); 8.15 (d,1H); 8.10 (s,1H); 8.00 (d,1H); 7.81 (dd,1H); 7.72 (d,1H); 7.66 (d,1H); 7.64-7.52 (m,4H); 7.46 (dd,1H); 4.11 (dt,1H); 1.83 (dq,2H); 0.98 (t,3H).
28	Calcd. C,78.24; H,5.47; N,7.60 Found C,78.49; H,5.58; N,7.41	3260; 1645; 1590; 1550	368 (M+.); 337; 232; 204	9.22 (d,1H); 8.33 (d,2H); 8.18 (s,1H); 8.13 (d,2H); 7.81 (dd,1H); 7.64-7.51 (m,4H); 7.46 (d,2H); 7.37 (dd,2H); 7.28 (dd,1H); 5.21 (dt,1H); 5.05 (t,1H); 3.71 (dd,2H).
29	Calcd. C,81.93; H,6.05; N,7.64 Found C,81.79; H,6.06; N,7.62	3260; 1650; 1595; 1550	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
30	Calcd. C,76.08; H,5.40; N,6.83 Found C,75.88; H,5.37; N,7.08	3260; 1755; 1735; 1640; 1580; 1530	410 (M+.); 351; 261; 246; 217	9.70 (d,1H); 8.02 (d,1H); 7.76 (dd,1H); 7.70-7.47 (m,9H); 7.47-7.34 (m,3H); 6.82 (d,1H); 3.75 (s,3H); 2.32 (s br,3H).
31	Calcd. C,82.08; H,6.36; N,7.36 Found C,81.82; H,6.34; N,7.33	3220; 1630; 1550	380 (M+.); 351; 246; 217	(353 K): 9.00 (d,1H); 8.01 (d,1H); 7.37 (dd,1H); 7.60-7.48 (m,7H); 7.45 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5.10 (dt,1H); 2.28 (s,3H); 2.00-1.80 (m,2H); 1.00 (t,3H).
32	Calcd. C,69.69; H,4.45; N,6.50 Found C,69.58; H,4.49; N,6.49	3270; 1750; 1670; 1595; 1520	430 (M+.); 371;266; 238; 203	9.78 (d,1H); 8.29 (d,2H); 8.24 (d,1H); 8.19 (d,1H); 8.16 (s,1H); 7.73 (dd,1H); 7.61-7.49 (m,5H);7.47-7.36 (m,3H); 5.80 (d,1H); 3.79 (s,3H).
33	Calcd. C,76.49; H,5.40; N,6.82 Found C,76.74; H,5.40; N,6.88	3240; 1750; 1665; 1590; 1510; 1500	410 (M+.); 351; 246; 218	9.70 (d,1H); 8.26 (d,2H); 8.08 (s,1H); 8.03 (d,1H); 7.96 (s,1H); 7.68 (dd,1H); 7.60-7.50 (m,5H); 7.48-7.36 (m,3H); 5.80 (d,1H); 3.79 (s,3H); 2.50 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 µA)	300 MHz ^1H NMR (DMSO), 303 K
34	Calcd. C,78.51; H,5.79; N,7.32, Found C,78.78; H,5.78; N,7.23	3220; 1740; 1695; 1535	382 (M+.); 337; 232; 204	9.35 (d,1H); 8.32 (d,2H); 8.14 (d,1H); 8.11 (d,1H); 8.10 (s,1H); 7.84 (dd,1H); 7.64 (dd,1H); 7.61-7.54 (m,3H); 7.50 (d,2H); 7.40 (dd,2H); 7.30 (dd,1H); 5.41 (dt,1H); 3.73-3.60 (m,2H); 3.36 (s,3H).
35	Calcd. C,69.69; H,4.45; N,6.50 Found C,70.27; H,4.46; N,6.45	3240; 1750; 1670; 1590; 1550; 1500	430 (M+.); 371; 266; 238; 203	9.80 (d,1H); 8.29 (d,2H); 8.27 (d,1H); 8.21 (s,1H); 8.16 (d,1H); 7.86 (dd,1H); 7.61-7.51 (m,5H); 7.48-7.38 (m,3H); 5.80 (d,1H); 3.75 (s,3H).
36	Calcd. C,76.40; H,5.70; N,6.60 Found C,76.44; H,5.72; N,6.62	3240; 1760; 1640; 1540	425 (MH+) •	(353 K): 9.52 (d,1H); 8.01 (d,1H); 7.89 (s br,1H); 7.74 (dd,1H); 7.60 (dd,1H); 7.54-7.48 (m,7H); 7.44-7.33 (m,3H); 4.88 (d,1H); 3.78 (s,3H); 2.91-2.68 (m,2H); 0.91 (t,3H).
37	Calcd. C,82.08; H,6.36; N,7.36 Found C,82.21; H,6.39; N,7.34	3300; 1635; 1590; 1545	380 (M+.); 337; 232; 204	9.28 (d,1H); 8.14 (d,1H); 8.07 (s,1H); 8.01 (d,1H); 7.82 (dd,1H); 7.64-7.51 (m,4H); 7.46 (d,2H); 7.39 (dd,2H); 7.28 (dd,1H); 5.15 (dt,1H); 1.94-1.69 (m,2H); 1.54-1.29 (m,2H); 0.95 (t,3H).
38	Calcd. C,82.20; H,6.64; N,7.10 Found C,82.34; H,6.64; N,7.07	3240; 1640; 1550	395 (MH+); CI; gas reagent methane; P 5000 mTorr; source 150 °C	(353 K): 8.91 (d,1H); 8.00 (d,1H); 7.71 (dd,1H); 7.68-7.48 (m,7H); 7.45 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.11 (dt,1H); 2.78-2.62 (m,2H); 2.00-1.80 (m,2H); 1.00 (t,3H); 0.90 (t br,3H).
39	Calcd. C,77.48; H,4.93; N,8.21 Found C,77.25; H,4.99; N,8.07	3330; 1790; 1720; 1665; 1530	511 (M+.); 482; 377; 349; 321	(353 K): 8.90 (d,1H); 8.20 (d,1H); 7.94 (dd,1H); 7.88-6,90 (m,5H); 7.74 (d,1H); 7.69 (dd,1H); 7.48-7.42 (m,2H); 7.36-7.31 (m,3H); 7.25-7.20 (m,2H); 7.18-7.10 (m,2H); 4.85 (dt,1H); 1.73 (ddq,1H); 0.82 (t,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
40	Calcd. C,82.32; H,6.91; N,6.86 Found C,82.02; H,6.95; N,6.90	3250; 1635; 1550	408 (M+.); 379, 289, 274; 246	(373 K): 8.72 (d,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.55-7.42 (m,9H); 7.38 (dd,2H); 7.28 (dd,1H); 5.15 (dt,1H); 2.66 (dd,2H); 1.94 (ddq,2H); 1.33 (m,2H); 1.01 (t,3H); 0.56 (t,3H).
41	Calcd. C,58.02; H,4.12; N,5.20; Br,29.69 Found C,58.14; H,4.18; N,5.22; Br,29.44	3250; 1650; 1540	537/539/541 (MH+) •	(353 K): 8.95 (d,1H); 7.96 (d,1H); 7.83 (dd,1H); 7.76 (d,1H); 7.71 (d,2H); 7.55 (d,2H); 7.45 (dd,2H); 7.39 (dd,2H); 7.30 (dd,1H); 5.10 (dt,1H); 2.92 (s,3H); 2.30 (s,3H); 1.88 (ddq,2H); 1.01 (t,3H).
42	Calcd. C,67.98; H,5.04; N,6.10; Br,17.39 Found C,68.04; H,5.02; N,6.05; Br,17.26	3260; 1640; 1540	459/461 (MH+) •	(353 K): 8.94 (d br,1H); 7.96 (d,1H); 7.81 (dd,1H); 7.76 (d,1H); 7.60-7.49 (m,4H); 7.45 (d,2H); 7.40 (dd,2H); 7.30 (dd,1H); 5.10 (dt,1H); 2.30 (s,3H); 1.89 (ddq,2H); 1.01 (t,3H).
43	Calcd. C,73.22; H,5.20; N,6.57 Found C,73.41; H,5.39; N,6.61	3200; 1750; 1665; 1620; 1520	426 (M+.); 367; 262; 234	9.70 (d,1H); 8.24 (d,2H); 8.08 (s,1H); 8.05 (d,1H); 7.61 (d,1H); 7.58-7.35 (m,9H); 5.80 (d,1H); 3.89 (s,3H); 3.74 (s,3H).
44	Calcd. C,74.30; H,4.62; N,6.42 Found C,74.28; H,4.61; N,6.41	3200; 1750; 1660; 1590; 1550; 1525; 1500	436 (M+.); 337; 272; 244	9.80 (d,1H); 8.18 (d,1H); 8.11 (d,1H); 8.09 (s,1H); 7.90 (s,1H); 7.87 (dd,1H); 7.80 (d,1H); 7.77 (d,1H); 7.67 (dd,1H); 7.54 (d,2H); 7.47-7.31 (m,5H); 5.80 (d,1H); 3.78 (s,3H).
45	Calcd. C,84.08; H,5.65; N,6.54 Found C,84.13; H,5.65; N,6.51	3320; 1635; 1590; 1530	337 (M-C_7H_7)+; 232; 204; 91	9.32 (ABXY,1H); 8.22 (d,2H); 8.09 (d,1H); 7.78 (dd,1H); 7.77 (s,1H); 7.64-7.52 (m,6H); 7.50-7.28 (m,9H); 5.53 (ABXY,1H); 3.20 (ABXY,1H); 3.16 (ABXY,1H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
46	Calcd. C,70.91; H,4.22; N,6.89; F,14.02 Found C,70.86; H,4.17; N,6.92; F,13.88	3300; 1655; 1590; 1540; 1500	406 (M+.); 386; 232; 204	10.15 (d,1H); 8.30 (dd,2H); 8.18 (d,1H); 8.10 (s,1H); 7.98 (d,1H); 7.86 (dd,1H); 7.75-7.42 (m,9H); 6.21 (m,1H).
47	Calcd. C,78.74; H,6.10; N,7.06 Found C,78.72; H,6.10; N,7.01	3250; 1635; 1550; 1500	396 (M+.); 367; 262; 219	9.24 (d,1H); 8.07 (d,1H); 7.97 (dd,2H); 7.76-7.70 (m,1H); 7.62-7.51 (m,5H); 7.46 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.10 (dt,1H); 3.52 (s,3H); 1.82 (dq,2H); 1.00 (t,3H).
48	Calcd. C,82.18; H,6.64; N,7.10 Found C,81.93; H,6.64; N,7.05	3250; 1630; 1540; 1500	394 (M+.); 365; 275; 260	(353 K): 8.90 (d br,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.56-7.42 (m,9H); 7.38 (dd,2H); 7.29 (dd,1H); 5.13 (dt,1H); 2.72 (m,2H); 1.90 (ddq,2H); 1.00 (t,3H); 0.90 (t br,3H).
49	Calcd. C,74.90; H,5.28; N,6.99; Found C,74.67; H,5.33; N,7.03;	3270; 1645; 1590; 1550; 1495; 770	400 (M+.); 371; 232; 204	9.20 (d,1H); 8.32 (d,2H); 8.08 (dd,2H); 8.06 (s,1H); 7.82 (t,1H); 7.65-7.40 (m,8H); 5.00 (dt,1H); 1.93-1.73 (m,2H); 0.98 (t,3H).
50	Calcd. C,76.08; H,5.40; N,6.82 Found C,76.16; H,5.42; N,6.84	1750; 1640; 1595;1550	411 (MH+); 232; 204•	8.32 (d,2H); 8.16 (d,1H); 8.10 (s,1H); 7.88 (dd,1H); 7.71 (dd,1H); 7.60-7.42 (m,9H); 3.86 (s,3H); 2.56 (s,3H).
51	Calcd. C,68.64; H,4.51; N,6.96 Found C,68.52; H,4.53; N,6.94	3290; 1740; 1640; 1590; 1530	402 (M+.); 343; 238; 210	9.72 (d,1H); 8.47 (dd,1H); 8.15 (d,1H); 8.07 (d,1H); 8.05 (s,1H); 7.96 (dd,1H); 7.81 (dd,1H); 7.71 (dd,1H); 7.62 (dd,1H); 7.53 (d,2H); 7.46-7.36 (m,3H); 5.78 (d,1H); 3.78 (s,3H).
52	Calcd. C,76.76; H,5.25; N,6.63 Found C,76.39; H,5.25; N,6.55	3250; 1750; 1660; 1590; 1520	422 (M+.); 258; 230	9.70 (d,1H); 8.45 (dd,1H); 8.18 (d,1H); 7.80-7.38 (m,11H); 5.83 (d,1H); 3.79 (s,3H); 3.20-2.80 (s br,4H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
53	Calcd. C,71.68; H,4.97; N,10.90 Found C,71.39; H,4.99; N,10.81	3410; 3250; 1740; 1678; 1600 *	385 (M+.); 221; 193	11.68 (s br,1H); 9.71 (d,1H); 8.17 (d,1H); 7.99 (d,1H); 7.86 (s,1H); 7.66 (dd,1H); 7.58-7.35 (m,6H); 7.00 (s br,2H); 6.22 (s br,1H); 5.75 (d,1H); 3.73 (s,3H).
54	Calcd. C,65.50; H,4.25; N,10.42 Found C,65.48; H,4.22; N,10.38	3300; 1755; 1645; 1585; 1530	344 (M-$COOCH_3$)+; 239; 211	9.82 (d,1H); 8.28 (s,1H); 8.19 (d,1H); 8.14 (d,1H); 8.10 (d,1H); 8.00 (d,1H); 7.88 (dd,1H); 7.73 (dd,1H); 7.53 (d,2H); 7.47-7.36 (m,3H); 5.80 (d,1H); 3.78 (s,3H).
55	Calcd. C,82.39; H,5.53; N,7.69 Found C,82.31; H,5.52; N,7.65	3240; 1640; 1590; 1545	365 (MH)+ •	9.20 (d,1H); 8.31 (d,2H); 8.27 (d,1H); 8.16 (s,1H); 8.14 (d,1H); 7.85 (dd,1H); 7.68 (dd,1H); 7.62-7-46 (m,4H); 7.32-7.23 (m,3H); 5.69 (dt,1H); 3.08-2.85 (m,2H); 2.64-2.52 (m,1H); 2.10-1.96 (m,1H).
56	Calcd. C,82.20; H,6.64; N,7.10 Found C,82.29; H,6.66; N,7.05	3270; 1640; 1590; 1540	394 (M+.); 337; 232; 204	9.12 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.07 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.64-7.52 (m,4H); 7.46 (d,2H); 7.39 (dd,2H); 7.28 (dd,1H); 5.13 (dt,1H); 1.96-1.71 (m,2H); 1.48-1.27 (m,4H); 0.9 (t,3H).
57	Calcd. C,76.08; H,5.40; N,6.82 Found C,75.92; H,5.44; N,6.77	3300; 1752; 1642; 1590; 1530	410 (M+.); 351; 246; 218; 203	9.74 (d,1H); 8.20 (d,2H); 8.18 (d,1H); 8.12 (d,1H); 8.08 (s,1H); 7.82 (dd,1H); 7.64 (dd,1H); 7.54 (d,2H); 7.47-7.36 (m,5H); 5.8 (d,1H); 3.79 (s,3H); 2.40 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
58	Calcd. C,82.53; H,7.39; N,6.42 Found C,82.59; H,7.45; N,6.39	3260; 1650; 1590; 1550; 1540	337 (M-C_7H_{15})+; 249; 232; 204	9.28 (d,1H); 8.29 (d,2H); 8.14 (d,1H); 8.07 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.64-7.52 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5,14 (dt,1H); 1.98-1.71 (m,2H); 1.30-1.20 (m,10H); 0.86 (t br,3H).
59	Calcd. C,76.08; H,5.40; N,6.82 Found C,76.21; H,5.40; N,6.79	3400-3100; 1742; 1665; 1590; 1530	410 (M+.); 261; 218	9.70 (d,1H); 8.22 (d,1H); 8.10 (d,1H); 7.84 (dd,1H); 7.70 (dd,1H); 7.67 (s,1H); 7.56 (d,1H); 7.50 (dd,2H); 7.45-7.33 (m,5H); 5.80 (d,1H); 3.78 (s,3H); 2.42 (s,3H).
60	Calcd. C,73.22; H,5.20; N,6.57 Found C,72.89; H,5.20; N,6.48	3300; 1750; 1645; 1590; 1520	426 (M+.); 367; 262; 234; 219; 191	9.72 (d,1H); 8.25 (d,2H); 8.17 (d,1H); 8.09 (d,1H); 8.07 (s,1H); 7.80 (dd,1H); 7.62 (dd,1H); 7.54 (dd,2H); 7.46-7.36 (m,3H); 7.12 (d,2H); 5.80 (d,1H); 3.89 (s,3H); 3.75 (s,3H).
61	Calcd. C,82.62; H,6.16; N,7.14 Found C,82.76; H,6.18; N,7.19	3230; 1640; 1590; 1550 *	392 (M+.); 249; 232, 204	9.00 (s,1H); 8.32 (dd,2H); 8,13 (d,1H); 8.05 (s,1H); 7.93 (d,1H); 7.81 (dd,1H); 7.64-7.52 (m,6H); 7.39 (dd,2H); 7.26 (dd,1H); 2.61-2.50 (m,2H); 2.10-2.00 (m,2H); 2.00-1.75 (m,4H).
62	Calcd. C,72.80; H,4.89; N,6.79 Found C,72.86; H,4.91; N,6.75	3500-3100; 1750; 1670; 1640; 1590	412 (M+.); 353; 248; 220	9.90 (s,1H); 9.70 (d,1H); 8.14 (d,2H); 8.14 (d,1H); 8.06 (d,1H); 8.01 (s,1H); 7.78 (dd,1H); 7.60 (dd,1H); 7.53 (dd,2H); 7.46-7.35 (m,3H); 6.94 (d,2H); 5.80 (d,3H); 3.75 (s,3H).
63	Calcd. C,70.90; H,4.58; N,6.36 Found C,70.73; H,4.59; N,6.35	3350; 1735; 1655; 1590	440 (M+.); 381; 276; 248	9.70 (d,1H); 8.17 (d,1H); 8.09 (d,1H); 8.06 (s,1H); 7.88 (d,1H); 7.85 (dd,1H); 7.80 (dd,1H); 7.62 (dd,1H); 7.42 (dd,2H); 7.46-7.36 (m,3H); 7.10 (d,2H); 6.13 (s,2H); 5.73 (d,1H); 3.73 (s.3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
64	Calcd. C,81.94; H,6.05; N,7.64 Found C,82.02; H,6.07; N,7.60	3220; 1640; 1590; 1545	366 (M+.); 351; 248; 232; 204	9.01 (s br,1H); 8.34 (dd,2H); 8.15 (s,1H); 8.13 (d,1H); 8.01 (d,1H); 7.81 (dd,1H); 7.66-7.52 (m,6H); 7.39 (dd,2H); 7.25 (dd,1H).
65	Calcd. C,82.07; H,6.36; N,7.36 Found C,82.15; H,6.36; N,7.41	3320; 1640; 1590; 1530	380 (M+.); 351; 232; 204	9.20 (d,1H); 8.29 (dd,2H); 8.14 (d,1H); 8.06 (s,1H); 8.03 (d,1H); 7.81 (dd,1H); 7.64-7.50 (m,4H); 7.34 (d,2H); 7.19 (d,2H); 5.00 (dt,1H); 2.30 (s,3H); 1.93-1.73 (m,2H); 0.98 (t,3H).
66	Calcd. C,71.68; H,4.97; N,10.90 Found C,70.42; H,4.99; N,10.56	3360; 3240; 1750; 1630; 1600; 1560	385 (M+.); 326; 221; 193	11.20 (s br,1H); 9.65 (d,1H); 8.05 (d,1H); 7.93 (d,1H); 7.78 (s,1H); 7.70 (dd,1H); 7.67 (m,1H); 7.55-7.34 (m,6H); 6.87 (m,1H); 6.80 (m,1H); 6.77 (d,1H); 3.75 (s,3H).
67	Calcd. C,64.53; H,3.90; N,6.02; Cl,15.24 Found C,64.59; H,3.95; N,5.94; Cl,15.03	3200; 1755; 1635; 1590; 1535	464 (M+.); 405; 300; 272; 237	9.70 (d,1H); 8.55 (d,1H); 8.30 (dd,1H); 8.22 (d,1H); 8.21 (s,1H); 8.17 (d,1H); 7.86 (dd,1H); 7.84 (d,1H); 7.70 (dd,1H); 7.54 (dd,2H); 7.47-7.36 (m,3H); 5.78 (d,1H); 3.74 (s,3H).
68		3300; 1635; 1590; 1530; 1495; 770	338; 337; 255; 233; 232; 204	9.18 (d br,1H); 8.35 (d,2H); 8.20 (s,1H); 8.13 (d,1H); 8.07 (d,1H); 7.81 (dd,1H); 7.63-7.51 (m,4H); 7.44 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5.08 (dt br,1H); 2.89 (d,2H); 1.60 (s br,2H).
69	Calcd. C,78.71; H,6.08; N,11.01 Found C,78.45; H,6.10; N,10.96	3490; 3380; 3260; 1630; 1600	381 (M+.); 352;247; 219; 218	9.20 (d,1H); 7.87 (m,1H); 7.70 (d,2H); 7.59-7.26 (m,11H); 5.08 (dt,1H); 4.80 (s br, 2H); 2.81 (dq,2H); 0.95 (t,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
70	Calcd. C,74.90; H,5.28; N,6.99; Cl,8.84 Found C,74.88; H,5.25; N,6.98; Cl,8.92	3230; 1640; 1550	400 (M+.); 371; 266; 238; 203	9.37 (d,1H), 8.10 (d,1H); 7.85 (dd,1H); 7.75-7.35 (m,12H); 5.07 (dt,1H);1.80 (dq,2H); 0.98 (t,,3H).
71	Calcd. C,67.42; H,4.75; N,6.29; Br,17.94 Found C,67.57; H,4.80; N,6.31; Br,18.00	3240; 1640; 1545	444/446 (M+.); 415/417; 310/312; 203	9.35 (d,1H); 8.10 (d,1H); 7.85 (dd br,1H); 7.70-7.30 (m,12H); 5.05 (dt,1H); 1.81 (dq,2H); 0.99 (t,3H).
72	Calcd. C,82.07; H,6.36; N,7.36 Found C,82.00; H,6.36; N,7.33	3240; 1630;1590; 1545	381 (MH)+ ; TSP, ammonium acetate (50 mM)/acetonitrile 60 : 40 as eluent; source 250 °C	9.24 (d,1H); 8.29 (d,2H); 8.14 (d,1H); 8.01 (s,1H); 7.96 (d,1H); 7.81 (dd,1H); 7.64-7.51 (m,4H); 7.47-7.36 (m,4H); 7.29 (dd,1H); 4.90 (dd,1H); 2.19-2.02 (m,1H);1.08 (d,3H); 0.80 (d,3H).
73	Calcd. C,81.94; H,6.05; N,7.64 Found C,79.33; H,5.82; N,7.34	3320; 1635; 1590; 1535	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
74	Calcd. C,81.94; H,6.05; N,7.64 Found C,82.08; H,6.09; N,7.59	3280; 1637; 1590; 1540	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
75	Calcd. C,72.45; H,4.62; N,6.76 Found C,72.28; H,4.59; N,6.79	3280; 1740; 1650; 1630; 1550	414 (M+.); 355; 250; 222	9.75 (d,1H); 8.28 (dd,2H); 8.21 (dd,1H); 8.2 (s,1H); 7.95 (dd,1H); 7.77 (ddd,1H); 7.61-7.50 (m,5H); 7.47-7.36 (m,3H); 5.80 (d,1H); 3.74 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 µA)	300 MHz ^1H NMR (DMSO), 303 K
76	Calcd. C,74.60; H,6.51; N,6.96 Found C,74.32; H,6.50; N,6.90	1740; 1665; 1595; 1535	402 (M+.); 238; 210	9.61 (d,1H); 8.11 (d,1H); 7.99 (d,1H); 7.75 (dd,1H); 7.59 (dd,1H); 7.50 (d,2H); 7.47-7.35 (m,4H); 5.74 (d,1H); 3.72 (s,3H); 2.90 (tt,1H); 2.00-1.20 (m,10H).
77	Calcd. C,69.69; H,4.45; N,6.50 Found C,69.81; H,4.45; N,6.54	3290; 1745; 1660; 1640; 1585; 1530	431 (MH+) •	9.71 (d,1H); 8.37 (s,1H); 8.30-8.15 (m,3H); 7.85 (dd,1H); 7.69 (dd,1H); 7.63-7.38 (m,8H); 5.79 (d,1H); 3.74 (s,3H).
78	Calcd. C,69.69; H,4.44; N,6.50 Found C,69.90; H,4.42; N,6.57	3290; 1745; 1660; 1600; 1520	431(MH+); TSP, ammonium acetate (0.1 M)/acetonitrile 60 : 40 as eluent; source 250 °C	9.70 (d,1H); 8.24 (d,1H); 8.14 (d,1H); 7.87 (dd,1H); 7.77 (s,1H); 7.76-7.62 (m,3H); 7.58-7.48 (m,4H); 7.44-7.34 (m,3H); 5.80 (d,1H); 3.72 (s,3H).
79	Calcd. C,78.51; H,5.80; N,7.32 Found C,78.55; H,5.82; N,7.26	3310; 3110; 1645; 1575; 1535	382 (M+.); 353; 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).
80	Calcd. C,71.36; H,4.88; N,6.16 Found C,71.39; H,4.88; N,6.17	3320; 1760; 1735; 1650; 1530	455 (MH)+ •	9.74 (d,1H); 8.24 (dd,2H); 8.17 (s,1H); 8.08 (dd,1H); 7.70-7.50 (m,7H); 7.46-7.35 (m,3H); 5.75 (d,1H); 3.75 (s,3H).
81	Calcd. C,72.80; H,4.89; N,6.79 Found C,73.24; H,5.00; N,6.42	3360; 3300; 1745; 1650; 1600; 1560;	413 (MH)+ •	9,69 (d,1H); 9.68 (s,1H); 8.49 (d,2H); 8.12 (s,1H); 7.64-7.35 (m,10H); 7.18 (d,1H); 5.79 (d,1H); 3.77 (s,3H).
82	Calcd. C,64.53; H,3.90; N,6.02 Found C,64.71; H,3.96; N,6.00	3240; 1740; 1645; 1595; 1550	464 (M+.); 405; 300; 272; 237	10.68 (d,1H); 8.25 (d,1H); 8.14 (d,1H); 7.88 (dd,1H); 7.82 (d,1H); 7.78 (s,1H); 7.74 (dd,1H); 7.74 (d,1H), 7.62 (dd,1H); 7.51 (d,2H); 7.44-7.33 (m,3H); 6.78 (d,1H); 3.74 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 µA)	300 MHz ^1H NMR (DMSO), 303 K
83	Calcd. C,66.89; H,4.72; N,6.24; Cl,7.90 Found C,66.53; H,4.74; N,6.10; Cl,7.48	3180; 1750; 1660; 1645; 1610; 1535; 1510	412 (M+.); 353; 232; 204	9.62 (d,1H); 8.28 (d,2H); 8.22 (d,1H); 8.16 (d,1H); 8.11 (s,1H); 7.86 (dd,1H); 7.68 (dd,1H); 7.61-7.51 (m,3H); 7.30 (d,2H); 6.80 (d,2H); 5.61 (d,1H); 3.71 (s,3H).
84	Calcd. C,84.03; H,5.35; N,6.76 Found C,83.27; H,5.64; N,7.05	3210; 1640; 1590; 1525	414 (M+.); 337; 232; 204	9.79 (d,1H); 8.30 (dd,2H); 8.15 (s,1H); 8.12 (d,1H); 8.02 (d,1H); 7.81 (dd,1H); 7.63-7.26 (m,14H); 6.52 (d,1H).
85	Calcd. C,78.51; H,5.80; N,7.33 Found C,78.49; H,5.84; N,7.26	3370; 1625; 1525	382 (M+.); 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).
86	Calcd. C,78.51; H,5.80; N,7.33 Found C,78.55; H,5.84; N,7.30	3270; 1650; 1630; 1570; 1535	382 (M+.); 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).
87	Calcd. C,72.80; H,4.89; N,6.79 Found C,72.12; H,4.88; N,6.63	3360; 1735; 1625; 1530	412 (M+.); 353; 248; 219	9.85 (s,1H); 9.63 (d br,1H); 7.97 (m,3H); 7.89 (d br,1H); 7.62-7.34 (m,10H); 5.75 (d,1H); 3.76 (s,3H).
88	Calcd. C,78.96; H,6.37; N,10.62 Found C,78.63; H,6.39; N,10.65	3320; 1640; 1590; 1525; 770	395 (M+.); 232; 204	9.15 (d,1H); 9.30 (d,2H); 9.18 (dd, 2H); 8.06 (s,1H); 7.80 (t,1H); 7.70-7.20 (m, 9H); 5.30 (dt,1H); 2.75 (dd,1H); 2.45 (dd,1H); 2.70 (s,6H).
89	Calcd. C,76.26; H,5.66; N,10.26 Found C,75.74; H,5.66; N,10.06	3280; 1660; 1635; 1590	409 (M+.); 337; 232; 204	9.40 (d,1H); 8.26 (d,2H); 8.22 (d,1H); 8.12 (d,1H); 8.05 (s,1H); 7.81 (dd,1H); 7.62 (dd,1H); 7.59-7.49 (m,5H); 7.43-7.33 (m,3H); 6.15 (d,1H); 3.00 (s,3H); 2.90 (s,3H).

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200°C; 70 eV; 200 μA)	300 MHz ^{1}H NMR (DMSO), 303 K
90	Calcd. C,75.57; H,5.02; N,11.02 Found C,75.23; H,5.12; N,10.88	3360; 3270; 1680; 1650; 1600	381 (M+.); 337; 232; 204	9.40 (d,1H); 8.31 (d,2H); 8,16 (s,1H); 8.15 (d,1H); 8,12 (d,1H); 7.81 (dd,1H); 7.78 (s br,1H); 7.64-7.50 (m,6H); 7.41-7.30 (m,3H); 7.23 (s br,1H); 5.71 (d,1H).
91	Calcd. C,77.22; H,5.79; N,9.65 Found C,76.91; H,5.87; N,9.56	3220; 1660; 1620; 1590	436 (MH+); TSP, ammonium acetate (0.1 M)/acetonitrile 60 : 40 as eluent; source 250° C	9.48 (d,1H); 8.27 (d,2H); 8.23 (d,1H); 8.12 (d,1H); 8.06 (s,1H); 8,02 (dd,1H); 7.63 (dd,1H); 7.60-7.50 (m,5H); 7.45-7.33 (m,3H); 5.92 (d,1H); 3.82-3.71 (m,1H); 3.53-3.26 (m,2H); 3.16-3.08 (m,1H); 1.98-1.68 (m,4H).
92	Calcd. C,68.82; H,4.57; N,6.69; Cl,8.46 Found C,68.42; H,4.60; N,6.56; Cl,8.22	1740; 1670; 1635; 1610; 1540	382 (M+.); 337; 204	9.64 (d,1H); 8.28 (d,2H); 8.22 (d,1H); 8.16 (d,1H); 8.13 (s,1H); 7.84 (dd,1H); 7.66 (dd,1H); 7.62-7.51 (m,5H); 7.46-7.34 (m,3H); 5.70 (d,1H).

* oil mull; • FAB POS, thioglycerol matrix, Xe gas, 8 KeV, source 50 °C.

EXAMPLE 93

(R,S)-N-[α-(Methoxycarbonyl)benzyl]-2-(p-chlorophenyl)quinoline-4-carboxamide

2 g (7.0 mmol) of 2-(p-chlorophenyl)quinoline-4-carboxylic acid and 1.7 ml (15.4 mmol) of N-methylmorpholine were dissolved, under nitrogen athmosphere, in 50 ml of dry THF.

The solution was cooled to -20°C and 0.91 ml (7.0 mmol) of isobutyl chloroformate were added. After 20 minutes, 2.12 g (10.5 mmol) of methyl (R,S) phenylglycinate hydrochloride and 1.3 ml (11.9 mmol) of N-methylmorpholine, dissolved in 30 ml of dry THF, were added and the reation mixture was stirred at room temperature overnight.

5 ml of H_2O were added and the reaction mixture was evaporated *in vacuo* to dryness. The residue was dissolved in Et_2O, washed with a saturated solution of $NaHCO_3$, separated, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.

The residual oil was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/isopropyl ether 7 : 3 to afford 0.9 g of crude product, which was recrystallized three times with $iPrO_2$/toluene to yield 0.5 g of the title compound.

$C_{25}H_{19}ClN_2O_3$

M.P. = 170-172 °C

M.W. = 430.90

Elemental analysis: Calcd. C, 69.72; H, 4.45; N, 6.50
Found C, 69.82; H, 4.47; N, 6.48

I.R. (KBr): 3280; 1740; 1670; 1635; 1590; 1530 cm^{-1}.

300 MHz 1H-NMR (DMSO-d6): 9.71 (d, 1H); 8.32 (d, 2H); 8.21 (d, 1H); 8.13 (d, 1H); 8.13 (s, 1H); 7.85 (dd, 1H); 7.67 (dd, 1H); 7.63 (d, 2H); 7.53 (dd, 2H); 7.46-7.38 (m, 3H); 5.79 (d, 1H); 3.74 (s, 3H).

MS (EI; source 200 °C;70 eV; 200 μA): 430 (M+.); 371; 266; 238; 203.

EXAMPLE 94

(R)-N-[α-(Methoxycarbonyl)-4-methoxybenzyl]-2-phenylquinoline-4-carboxamide

0.62 g (1.5 mmol) of (R)-N-[α-(methoxycarbonyl)-4-hydroxybenzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 83) were dissolved in 30 ml of dry acetone and 2 ml of dry DMF; 0.14 g (0.75 mmol) of K_2CO_3 were added and the reaction mixture was stirred for 30 minutes.

0.093 ml (1.5 mmol) of methyl iodide were added at room temperature and the reaction mixture was heated at 40 °C for 4 hours. 0.104 g (0.75 mmol) of K_2CO_3 and

0.093 ml (1.5 mmol) of methyl iodide were added again, and the mixture refluxed for additional 6 hours.

The mixture was evaporated *in vacuo* to dryness, dissolved in EtOAc and washed with H_2O. The organic layer, dried over Na_2SO_4, was evaporated *in vacuo* to dryness. The residue was recrystallized from Et_2O to yield 0.45 g of the title compound.

$C_{26}H_{22}N_2O_4$

M.P. = 160-162 °C

M.W. = 426.48

Elemental analysis: Calcd. C, 73.22; H, 5.20; N, 6.57
Found C, 73.01; H, 5.20; N, 6.48

I.R. (KBr): 3210; 1750; 1635; 1625; 1590; 1530; 1515 cm^{-1}

300 MHz 1H-NMR (DMSO-d6): 9.65 (d, 1H); 8.28 (d, 2H); 8.21 (d, 1H); 8.14 (d, 1H); 8.10 (s, 1H); 7.84 (dd, 1H); 7.67 (dd, 1H); 7.61-7.49 (m, 3H); 7.44 (d, 2H); 6.98 (d, 2H); 4.70 (d, 1H); 3.79 (s, 3H); 3.76 (s, 3H).

MS (EI; source 200 °C;70 eV; 200 μA): 426 (M+.); 367; 232; 204.

EXAMPLE 95

(R,S)-N-[α-(Methoxycarbonyl)-α-(methyl)benzyl]-N-methyl-2-phenylquinoline-4-carboxamide hydrochloride

0.50 g (1.3 mmol) of (R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 4) were dissolved, under nitrogen athmosphere, in 10 ml of dry DMF.

The solution was cooled to 0 °C and 0.052 g (1.3 mmol) of NaH (60%) were added; after 20 minutes at 0 °C the temperature was raised to r.t. and 0.09 ml (1.4 mmol) of MeI were added. The reation mixture was stirred at room temperature overnight, then the procedure was repeated by adding additional 0.052 g (1.3 mmol) of NaH (60%) and 0.1 ml (1.6 mmol) of MeI.

After 6 hours at room temperature, 10 ml of saturated solution of NH_4Cl were added and the reaction mixture was evaporated *in vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with water; the organic layer was separated, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.

The residual oil was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/ethyl acetate 3 : 2 containing 0.5% of conc. NH_4OH to afford 0.18 g of a crude product which was dissolved in Et_2O and treated with HCl/Et_2O to yield 0.15 g of the title compound.

$C_{27}H_{24}N_2O_3.HCl$

M.W. = 460.96

I.R. (KBr): 1745; 1640; 1610 cm^{-1}.
MS (EI; source 200 °C;70 eV; 200 μA): 424 (M+.); 365; 232; 204.

EXAMPLE 96

(R,S)-N-[α-(Methylcarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

0.27 ml (3.1 mmol) of oxalyl chloride were dissolved, under nitrogen athmosphere, in 2.3 ml of dry CH_2Cl_2.
The solution was cooled to -55 °C and 0.22 ml (3.1 mmol) of DMSO, dissolved in 0.7 ml of dry CH_2Cl_2, were added dropwise maintaining the temperature below -50 °C. The reaction was stirred at -55°C for 7 minutes then 0.97 g (2.5 mmol) of (R,S)-N-[α-(1-hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 17), dissolved in 25 ml of dry CH_2Cl_2, were added keeping the temperature between -50 and -55 °C.
After 30 minutes at -55 °C, 1.9 ml (13.6 mmol) of TEA were added without exceeding -40 °C, then the reaction mixture was allowed to reach room temperature and stirred for additional 15 minutes.
The reaction was quenched with 5 ml of H_2O and extracted with CH_2Cl_2; the organic layer was washed with H_2O, 20% citric acid, saturated solution of $NaHCO_3$ and brine; the organic layer was separated, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.
The residual oil was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/ethyl acetate 70 : 30 containing 0.5% of conc. NH_4OH to afford 0.64 g of a crude product which was triturated with warm *i*-Pr_2O/*i*-PrOH 2 : 1, filtered, washed and dried to yield 0.5 g of the title compound.
$C_{25}H_{20}N_2O_2$
M.P. = 160-161 °C
M.W. = 380.45
Elemental analysis: Calcd. C, 78.93; H, 5.30; N, 7.36;
Found C, 79.01; H, 5.31; N, 7.27.
I.R. (KBr): 3400; 3265; 1725; 1660; 1640; 1592 cm^{-1}.
300 MHz 1H-NMR (DMSO-d6): 9.60 (d, 1H); 8.29 (d, 2H); 8.17 (d, 1H); 8.14 (d, 1H); 8.12 (s, 1H); 7.82 (dd, 1H); 7.65 (dd, 1H); 7.61-7.51 (m, 5H); 7.48-7.36 (m, 3H); 2.19 (s, 3H).
MS (EI; source 200 °C;70 eV; 200 μA): 380 (M+.); 337; 232; 204.

EXAMPLE 97

(R,S)-N-[α-(2-Hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide

0.7 g (1.7 mmol) of (R,S)-N-[α-(methoxycarbonylmethyl)benzyl]-2-phenylquinoline-

4-carboxamide (compound of Ex. 15) were dissolved, under nitrogen athmosphere, in 50 ml of *t*-BuOH and 2 ml of MeOH.

60 mg (1.6 mmol) of $NaBH_4$ were added in 15 minutes to the boiling solution. The reaction mixture was refluxed for 6 hours, quenched with 5 ml of saturated solution of NH_4Cl and then evaporated *in vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with brine; the organic layer was separated, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.

The crude product was flash chromatographed on 230-400 mesh silica gel, eluting with Et_2O containing 0.5% of conc. NH_4OH and then crystallized from *i*-PrOH to yield 0.19 g of the title compound.

$C_{25}H_{22}N_2O_2$

M.P. = 167-169 °C

M.W. = 382.47

Elemental analysis: Calcd. C, 78.52; H, 5.80; N, 7.32;
Found C, 78.49; H, 5.79; N, 7.29.

I.R. (KBr): 3360; 1650; 1592 cm^{-1}.

300 MHz 1H-NMR (DMSO-d6): 9.30 (d, 1H); 8.31 (d, 2H); 8.13 (d, 1H); 8.10 (s, 1H); 8.03 (d, 1H); 7.81 (dd, 1H); 7.64-7.51 (m, 4H); 7.46 (d, 2H); 7.39 (dd, 2H); 7.29 (dd, 1H); 5.30 (dt, 1H); 4.61 (t, 1H); 3.61-3.41 (m, 2H); 2.11-1.86 (m, 2H).

MS (EI; source 200 °C;70 eV; 200 μA): 382 (M+.); 337; 232; 204.

EXAMPLE 98

(S)-N-(α-Ethylbenzyl)-3-(2-dimethylaminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

0.62 g (1.6 mmol) of (S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Ex. 85) were dissolved in 30 ml of dry DMF.

0.58 g (4.0 mmol) of dimethylaminoethylchloride hydrochloride and 0.56 g (4.0 mmol) of K_2CO_3 were added and the reaction mixture was refluxed for 20 hours.

The K_2CO_3 was filtered off and the mixture was evaporated *in vacuo* to dryness, dissolved in AcOEt and washed with H_2O and with 20% citric acid. The aqueous layer was made alkaline with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.

The residue was flash chromatographed on 230-400 mesh silica gel, eluting with CH_2Cl_2/MeOH 98 : 2 containing 0.4% of conc. NH_4OH and then with CH_2Cl_2/MeOH 86 : 10 containing 0.6% of conc. NH_4OH to yield 85 mg of a crude product which was dissolved in EtOAc and treated with HCl/Et_2O to obtain 75 mg of

the title compound.

$C_{29}H_{31}N_3O_2.HCl$

M.P. = 70 °C dec.

M.W. = 490.05

I.R. (nujol): 3600; 3100; 1650; 1550 cm^{-1}.

300 MHz 1H-NMR (DMSO-d6): 10.28 (s br, 1H); 9.50 (d, 1H); 8.10 (d, 1H); 7.96 (dd, 2H); 7.78 (m, 1H); 7.67-7.61 (m, 2H); 7.61-7.51 (m, 3H); 7.49-7.39 (m, 4H); 7.33 (dd, 1H); 5.08 (dt, 1H); 3.90 (t, 2H); 2.96 (dt, 2H); 2.49 (s, 6H); 1.85 (m, 2H); 0.97 (t, 3H).

MS (FAB POS, thioglycerol matrix, Xe gas, 8 KeV, source 50 °C): 454 (MH+)

EXAMPLE 99

(S)-N-(α-Ethylbenzyl)-3-acetylamino-2-phenylquinoline-4-carboxamide

0.40 g (1.05 mmol) of (S)-N-(α-ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (compound of Ex. 69) were heated in 25 ml of acetic anhydride at 70 °C for 1 hour and then at 100 °C for additional 3 hours.

The reaction mixture was then evaporated *in vacuo* to dryness and the residue dissolved in EtOAc; the solution was washed with water, saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated *in vacuo* to dryness.

The crude product (0.39 g) was purified by silica gel flash column chromatography, eluting with a mixture of hexane/EtOAc/conc. NH_4OH, 70 : 30 : 0.5, respectively, to afford 0.2 g of a pure compound which was recrystallized from acetone to yield 0.14 g of the title compound.

$C_{27}H_{25}N_3O_2$

M.P. = 268-269 °C

M.W. = 423.52

Elemental analysis: Calcd. C, 76.57; H, 5.95; N, 9.92;
Found C, 76.38; H, 5.98; N, 9.90.

I.R. (KBr): 3230; 1670; 1640; 1555; 1525 cm^{-1}.

300 MHz 1H-NMR (DMSO-d6): 9.65 (s, 1H); 9.05 (d, 1H); 8.10 (d, 1H); 7.80 (t, 1H); 7.70-7.50 (m, 4H); 7.45-7.20 (m, 8H); 5.08 (dt, 1H); 1.85 (m, 2H); 1.60 (s, 3H); 0.97 (t, 3H).

MS (EI; source 200 °C;70 eV; 200 μA): 423 (M+.); 381; 334; 289; 261; 247; 218.

EXAMPLE 100

(-)-(S)-N-(α-Ethylbenzyl)-3-(3-dimethylaminopropoxy)-2-phenylquinoline-4-carboxamide hydrochloride

1.2 g (3.1 mmol) of (-)-(S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Ex. 85) were dissolved in 15 ml of dry THF.
1.0 g (8.2 mmol) of 3-dimethylaminopropylchloride, dissolved in 10 ml of Et_2O, 1.3 g (9.4 mmol) of K_2CO_3 and 0.16 g of KI were added and the reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 2 hours.
Further 0.77 g (6.3 mmol), 1.0 g (8.2 mmol), 0.6 g (4.9 mmol) and additional 0.6 g (4.9 mmol) of 3-dimethylaminopropylchloride, dissolved each time in 10 ml of Et_2O, and some KI were added every 12 hours and the reaction refluxed.
The K_2CO_3 was filtered off and the mixture was evaporated *in-vacuo* to dryness, dissolved in EtOAc and washed with H_2O and with 20% citric acid. The aqueous layer was made alkaline with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness.
The residue was flash chromatographed on 230-400 mesh silica gel, eluting with CH_2Cl_2/MeOH 95: 5 containing 0.5% of conc. NH_4OH to yield 0.9 g of a crude product which was dissolved in EtOAc and treated with HCl/Et_2O to obtain 0.62 g of the title compound.

$C_{30}H_{33}N_3O_2$.HCl
M.P. = 108°C dec.
M.W. = 504.08
$[\alpha]_D^{20}$ = - 16.0 (c = 0.5, MeOH)
I.R. (KBr): 3400; 3080; 1655; 1545 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 10.55 (s br, 1H); 9.35 (d, 1H); 8.09 (d, 1H); 7.92 (dd, 2H); 7.76 (ddd, 1H); 7.65-7.51 (m, 5H); 7.48-7.40 (m, 4H); 7.31 (dd, 1H); 5.10 (dt, 1H); 3.72-3.62 (m, 2H); 2.75-2.60 (m, 2H); 2.58 (d, 3H); 2.56 (d, 3H); 1.90-1.67 (m, 4H); 1.00 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 467 (M+.); 466; 395; 58.

EXAMPLE 101

(-)-(S)-N-(α-Ethylbenzyl)-3-[2-(1-phthaloyl)ethoxy]-2-phenylquinoline-4-carboxamide hydrochloride

1.9 g (5.0 mmol) of (-)-(S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Ex. 85) were dissolved in 20 ml of dry THF.

3.8 g (14.9 mmol) of 2-phthalimidoethylbromide, dissolved in 15 ml of THF, 2.0 g (14.5 mmol) of K_2CO_3 and 0.25 g of KI were added and the reaction mixture was stirred at room temperature for 2.5 hours and then refluxed for 2 hours.

1.9 g (7.4 mmol) of 2-phthalimidoethylbromide and some KI were added and the reaction was refluxed for additional 3.5 hours.

0.5 g (2.0 mmol) of 2-phthalimidoethylbromide and some KI were added again and the mixture was refluxed for 5 hours.

The K_2CO_3 was filtered off and the mixture was evaporated *in-vacuo* to dryness, dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated *in-vacuo* to dryness.

The residue was flash chromatographed on 230-400 mesh silica gel, eluting with hexane/EtOAc 80 : 20 containing 0.5% of conc. NH_4OH and then hexane/EtOAc 60 : 40 containing 0.5% of conc. NH_4OH to afford 2.6 g of a purified product which was triturated with iPr_2O to yield 2.5 g of the title compound.

$C_{35}H_{29}N_3O_4$

M.P. = 172-175°C

M.W. = 555.64

$[\alpha]_D^{20}$ = - 16.3 (c = 0.5, MeOH)

I.R. (KBr): 3280; 3060; 2960; 1780; 1715; 1660; 1530 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.27 (d, 1H); 8.03 (d, 1H); 7.92-7.84 (m, 4H); 7.78-7.69 (m, 3H); 7.60-7.53 (m, 2H); 7.46-7.38 (m, 4H); 7.27 (dd, 1H); 7.13-7.04 (m, 3H); 4.96 (dt, 1H); 3.92-3.78 (m, 2H); 3.72-3.55 (m, 2H); 1.78 (dq, 2H); 0.93 (t, 3H).

MS (EI; source 180 °C; 70 V; 200 mA): 555 (M+.), 526, 421, 174.

EXAMPLE 102

(-)-(S)-N-(α-Ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

2.2 g (3.9 mmol) of (-)-(S)-N-(α-ethylbenzyl)-3-[2-(1-phthaloyl)ethoxy]-2-phenyl quinoline-4-carboxamide hydrochloride (compound of Ex. 101) were dissolved in 150 ml of 96% EtOH and 0.38 ml (7.8 mmol) of hydrazine hydrate were added to the boiling solution, which was then refluxed for 4 hours.

Further 0.4 ml (8.2 mmol), 0.2 ml (4.1 mmol), 0.2 ml (4.1 mmol), 0.4 ml (8.2 mmol) and 0.4 ml (8.2 mmol) of hydrazine hydrate were added every 12 hours and the reaction mixture was maintained refluxed.

The reaction mixture was then evaporated *in-vacuo* to dryness, dissolved in 20 ml H_2O, cooled and acidified with 10 ml conc. HCl.

The mixture was boiled for 1 hour and cooled; the phthalydrazide was filtered off. The aqueous layer was washed with EtOAc and then made alkaline with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness.

The residue was flash chromatographed on 230-400 mesh silica gel, eluting with EtOAc/MeOH 96: 4 containing 1.2% of conc. NH_4OH to afford a purified product which was dissolved in EtOAc and treated with HCl/Et_2O to yield 1.2 g of the title compound.

$C_{27}H_{27}N_3O_2.HCl$
M.P. = 119°C dec.
M.W. = 462.00
$[\alpha]_D^{20}$ = - 19.4 (c = 0.5, MeOH)
I.R. (KBr): 3400; 3080; 1640; 1545 cm^{-1}.
300 MHz ^1H-NMR (DMSO-d_6): δ 9.45 (d, 1H); 8.09 (d, 1H); 8.00 (dd, 1H); 7.94 (s br, 3H); 7.76 (ddd, 1H); 7.65-7.51 (m, 4H); 7.48-7.40 (m, 3H); 7.31 (dd, 1H); 5.09 (dt, 1H); 3.83 (t, 2H); 2.72 (m, 2H); 1.93-1.80 (m, 2H); 0.99 (t, 3H).
MS (FAB POS, thioglycerol matrix; Xe gas, 8 keV; source 50 °C): 426 (MH+).

EXAMPLE 103

(+)-(S)-N-(α-Ethylbenzyl)-3-[2-(1-pyrrolidinyl)ethoxy]-2-phenylquinoline-4-carboxamide hydrochloride

2.0 g (5.2 mmol) of (-)-(S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (compound of Ex. 85) were dissolved in 25 ml of dry THF.
1.0 g (7.5 mmol) of 2-pyrrolidinoethylchloride and 2.2 g (15.9 mmol) of K_2CO_3 were added and the reaction mixture was stirred at room temperature for 30 minutes and then refluxed; 1.1 g (8.2 mmol) of 2-pyrrolidinoethylchloride were added to the boiling solution which was refluxed overnight.
The K_2CO_3 was filtered off and the mixture was evaporated *in-vacuo* to dryness, dissolved in EtOAc and washed with H_2O and 20% citric acid. The aqueous layer was made alkaline with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness.
The residue was flash chromatographed on 230-400 mesh silica gel, eluting with CH_2Cl_2/MeOH 97: 3 containing 0.5% of conc. NH_4OH to yield 1.8 g of a purified product which was dissolved in EtOAc and treated with HCl/Et_2O to yield 2.0 g of the title compound.

$C_{31}H_{33}N_3O_2$. HCl
M.P. = 110-115 °C (dec.)
M.W. = 516.08
$[\alpha]_D^{20}$ = + 4.5 (c = 0.5, MeOH)
I.R. (KBr): 3400; 3080; 1655; 1545 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 10.50 (s br, 1H); 9.50 (d, 1H); 8.10 (d, 1H); 7.96 (dd, 2H); 7.78 (ddd, 1H); 7.68-7.30 (m, 10H); 5.10 (dt, 1H); 3.90 (m, 2H); 3.20 (m, 2H); 3.00 (m, 2H); 2.65 (m, 2H); 1.95-1.65 (m, 6H); 1.94 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 479 (M+.); 478; 383; 97; 84.

EXAMPLE 104

(-)-(S)-N-(α-Ethylbenzyl)-3-(dimethylaminoacetylamino)-2-phenylquinoline-4-carboxamide

1.1 g (2.8 mmol) of (-)-(S)-N-(α-ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (compound of Ex. 69) were dissolved, under nitrogen atmosphere, in 10 ml of warm toluene. 0.96 g (5.6 mmol) of chloroacetic anhydride, dissolved in 5 ml of toluene, were dropped and the solution was refluxed for 1 hour.
The reaction mixture was evaporated *in-vacuo* to dryness, suspended in 10 ml of CH_2Cl_2 and dropped in 5 ml of ice-cooled 28% Me_2NH/EtOH.
The solution was stirred at room temperature overnight, then 15 ml of 28% Me_2NH/EtOH were added and the reaction mixture was heated at 60 °C in a parr apparatus.
The mixture was evaporated *in-vacuo* to dryness, dissolved in 20% citric acid and washed with EtOAc. The aqueous layer was basified with 2 N NaOH and extracted with EtOAc; the organic layer was washed with brine, separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to afford 1.4 g of the crude product.
This product was triturated with warm *i*-Pr_2O to yield 0.86 g of the title compound.

$C_{29}H_{30}N_4O_2$
M.P. = 189-191 °C
M.W. = 466.59
$[\alpha]_D^{20}$ = - 63.1 (c = 0.5, MeOH)
I.R. (KBr): 3230; 3180; 1670; 1630; 1540 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.41 (s, 1H); 8.97 (d, 1H), 8.08 (d, 1H); 7.81 (dd, 1H); 7.70-7.59 (m, 4H); 7.49-7.26 (m, 8H); 5.00 (dt, 1H); 2.55 (s, 2H); 1.97 (s, 3H); 1.90-1.65 (m, 2H); 0.93 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 466 (M+.); 331; 58.

EXAMPLE 105

N-(α,α-Dimethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide

2.0 g (7.5 mmol) of 3-hydroxy-2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen atmosphere, in 70 ml of dry THF and 30 ml of CH_3CN.

1.02 g (7.5 mmol) of cumylamine and 1.12 g (8.3 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at -10°C.

1.71 g (8.3 mmol) of DCC, dissolved in 20 ml of CH_2Cl_2, were added dropwise and the solution was kept at -5°- 0°C for 2 hours and then at room temperature overnight. The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and brine.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 20 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness to obtain 1.4 g of a crude product which was flash chromatographed on 230-400 mesh silica gel, eluting initially with hexane/EtOAc 9/1 and then hexane/EtOAc 8/2 to afford 0.4 g of the purified product which was recrystallized twice from *i*-PrOH to yield 0.15 g of the title compound.

$C_{25}H_{22}N_2O_2$

M.P. = 166-169°C dec.

M.W. = 382.47

I.R. (nujol): 3200; 1650; 1580; 1535 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.56 (s, 1H); 8.92 (s br, 1H); 8.00-7.94 (m, 3H); 7.76 (d br, 1H); 7.63-7.45 (m, 7H); 7.36 (dd; 2H); 7.24 (dd, 1H); 1.72 (s, 6H).

MS (EI; source 180 °C; 70 V; 200 mA): 382 (M+.); 264; 247; 219; 119.

EXAMPLE 106

N-(α,α-Dimethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide

2.0 g (7.6 mmol) of 3-amino-2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen atmosphere, in 70 ml of dry THF and 30 ml of CH_3CN.

1.02 g (7.6 mmol) of cumylamine and 1.12 g (8.3 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at -10°C.

1.72 g (8.3 mmol) of DCC, dissolved in 20 ml of CH_2Cl_2, were added dropwise and the solution was kept at -5°- 0°C for 2 hours and then at room temperature overnight. The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and brine.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 20 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness to obtain 2.0 g of a crude product which was flash chromatographed on 230-400 mesh silica gel, eluting with hexane/EtOAc 6/4 containing 1% of conc. NH_4OH to afford 0.9 g of the purified product which was recrystallized from hexane/EtOAc 1/1 and then from *i*-PrOH to yield 0.45 g of the title compound.

$C_{25}H_{23}N_3O$

M.P. = 166-168°C

M.W. = 381.48

I.R. (nujol): 3460; 3360; 3220; 1667; 1605; 1527 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.05 (s, 1H); 7.87 (dd, 1H); 7.74-7.68 (m, 3H); 7.60-7.42 (m, 7H); 7.37 (dd, 2H); 7.24 (dd, 1H); 4.74 (s, 2H); 1.71 (s,6H).

MS (EI; source 180 °C; 70 V; 200 mA): 381 (M+.); 263; 218; 119.

EXAMPLE 107

(-)-(S)-N-(α-Ethylbenzyl)-5-methyl-2-phenylquinoline-4-carboxamide

0.80 g (3.04 mmol) of 5-methyl-2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen atmosphere, in 30 ml of dry THF and 12 ml of CH_3CN.

0.43 g (3.20 mmol) of (S)-(-)-α-ethylbenzylamine and 0.78 g (5.78 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at -10°C.

0.69 g (3.34 mmol) of DCC, dissolved in 5 ml of CH_2Cl_2, were added dropwise and the solution was kept at -5°- 0°C for 2 hours and then at

room temperature overnight. The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and brine.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 10 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness to obtain 1.15 g of a crude product which was flash chromatographed on 230-400 mesh silica gel, eluting with hexane/EtOAc 6/2 containing 0.5% of conc. NH_4OH to afford 0.47 g of the purified product which was recrystallized from i-Pr_2O containing some drops of EtOAc to yield 0.36 g of the title compound as a white powder.

$C_{26}H_{24}N_2O$
M.P. = 189-192 °C
M.W. = 380.49
$[\alpha]_D^{20}$ = - 3.8 (c = 0.5, MeOH)
I.R. (KBr): 3280; 3070; 3020; 1635; 1545 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.20 (d, 1H); 8.23 (d, 2H); 7.93 (d, 1H); 7.78 (s, 1H); 7.20-7.70 (m, 10H); 5.00 (dt, 1H); 2.38 (s broad, 3H); 1.70-1.90 (m, 2H); 0.95 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 380 (M+.); 246; 218.

EXAMPLE 108

(R,S)-N-[α-(1-Hydroxyethyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide

Prepared as described in Ex. 1, starting from 11.08 g (39.33 mmol) of crude 3-methyl-2-phenylquinoline-4-carbonylchloride, 4.87 g (32.20 mmol) of 1-phenyl-2-hydroxypropylamine and 10.33 ml (74.14 mmol) of TEA in 150 ml of a 1:1 mixture of dry CH_2Cl_2 and CH_3CN.

The precipitated TEA hydrochloride was filtered off and the filtrate concentrated *in-vacuo* to dryness; the residue was dissolved in CH_2Cl_2 (100 ml) and washed with a sat. sol. of $NaHCO_3$, 20 % citric acid and brine. The organic solution was dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to obtain 13.23 g of an oil, which was crystallized from *i*-PrO_2 (100 ml) containing 6 ml of *i*-PrOH to yield 9.14 g of the title

compound as an off-white solid.

$C_{26}H_{24}N_2O_2$
M.P. = 163-165 °C
M.W. = 396.49
I.R. (nujol): 3400; 3260; 1635; 1580 cm^{-1}.

EXAMPLE 109

(R,S)-N-[α-(Methylcarbonyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide

Prepared as described in Example 96, starting from 3.25 g (25.60 mmol) of oxalyl chloride, 3.88 g (49.66 mmol) of DMSO, 8.2 g (20.68 mmol) of (R,S)-N-[α-(1-hydroxyethyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide (compound of Ex. 108) and 15.72 ml (112.76 mmol) of TEA in 230 ml of dry CH_2Cl_2.
The reaction was quenched with 40 ml of H_2O and the organic layer separated and washed with 20% citric acid, sat. sol. $NaHCO_3$ and brine. The organic solution was dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to afford 9.4 g of the crude title compound as an oil. This residual oil was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/ethyl acetate 70 : 30 containing 1% of conc. NH_4OH to afford 7.7 g of the purified product which was crystallized from a mixture of EtOAc/hexane 1 : 3 respectively, to yield 6.0 g of the pure title compound.

$C_{26}H_{22}N_2O_2$
M.P. = 156-158 °C
M.W. = 394.48
I.R. (nujol): 3270; 3180; 1735; 1725; 1660; 1630; 1527; 1460 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.53 (d, 1H); 8.01 (d, 1H); 7.73 (dd, 1H); 7.62-7.35 (m, 12H); 5.97 (d, 1H); 2.30 (s br, 3H); 2.18 (s, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 394 (M+.); 352; 351; 246; 218; 217.

EXAMPLE 110

(R,S)-N-[α-(Ethyl)-4-pyridylmethyl]-2-phenylquinoline-4-carboxamide

4.12 g (16.52 mmol) of 2-phenylquinoline-4-carboxylic acid were dissolved,

under nitrogen atmosphere, in 40 ml of dry CH_2Cl_2 and 30 ml of THF.
1.50 g (11.01 mmol) of 1-(4-pyridyl)-*n*-propyl amine and 2.23 g (16.52 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at 0°C.
3.41 g (16.52 mmol) of DCC, dissolved in 26 ml of dry CH_2Cl_2, were added dropwise and the solution was kept at 0°C for 2 hours and then stirred at room temperature for 36 hours. The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in 100 ml of CH_2Cl_2 and washed with H_2O, 10% K_2CO_3, 5% citric acid and brine.
The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 30 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.
The solution was evaporated *in-vacuo* to dryness to obtain 3.5 g of a crude product which was recrystallized three times from *i*-PrOH to yield 0.91 g of the title compound.

$C_{24}H_{21}N_3O$
M.P. = 218-219 °C
M.W. = 367.45
I.R. (KBr): 3260; 3060; 1648; 1595; 1545; 1350 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.33 (d, 1H); 8.58 (d, 2H); 8.33 (dd, 2H); 8.15 (d, 1H); 8.14 (s, 1H); 8.03 (d, 1H); 7.82 (dd, 1H); 7.66-7.52 (m, 4H); 7.47 (d, 2H); 5.05 (dt, 1H); 1.85 (dq, 2H); 1.00 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 367 (M+.); 338; 232; 204.

EXAMPLE 111

(R,S)-N-[α-(Ethyl)-2-thienylmethyl]-2-phenylquinoline-4-carboxamide

1.40 g (8.00 mmol) of 1-(2-thienyl)-*n*-propyl amine hydrochloride and 2.45 ml (17.60 mmol) of TEA were dissolved, under nitrogen atmosphere, in 50 ml of dry CH_2Cl_2 and 30 ml of CH_3CN.
2.0 g (8.00 mmol) of 2-phenylquinoline-4-carboxylic acid and 1.30 g (9.60 mmol) of N-hydroxybenzotriazole (HOBT) were added.
2.48 g (12.00 mmol) of DCC, dissolved in 30 ml of dry CH_2Cl_2, were added dropwise and the solution was stirred at room temperature for 36 hours.

50 ml of 10% HCl were added and the solution stirred for aditional 2 hours. The precipitated dicyclohexylurea was filtered off and the organic layer washed with 10% citric acid and 10% K_2CO_3.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness. The crude product was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of hexane/EtOAc/CH_2Cl_2 80 : 15 : 0.5 to afford 2.0 g of a yellow oil which was crystallized from a mixture of toluene/hexane to yield 0.9 g of the pure title compound as white crystals.

$C_{23}H_{20}N_2OS$
M.P. = 134-137 °C
M.W. = 372.49
I.R. (KBr): 3230; 3060; 1630; 1590; 1545 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.33 (d, 1H); 8.30 (dd, 2H); 8.15 (d, 1H); 8.13 (d, 1H); 8.08 (s, 1H); 7.84 (ddd, 1H); 7.68-7.51 (m, 4H); 7.44 (dd, 1H); 7.11 (d, 1H); 7.02 (dd, 1H); 5.33 (dt, 1H); 2.10-1.88 (m, 2H); 1.05 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 372 (M+.); 343; 232; 204.

EXAMPLE 112

(+)-(S)-N-(α-Ethylbenzyl)-3-dimethylaminomethyl-2-phenylquinoline-4-carboxamide hydrochloride

5.60 g (21.27 mmol) of 3-methyl-2-phenylquinoline-4-carboxylic acid were dissolved in 100 ml of dichloroethane.

7.60 g (42.50 mmol) of N-bromosuccinimide and 0.52 g (2.00 mmol) of dibenzoyl peroxide were added and the solution refluxed for 24 hours.

The reaction mixture was evaporated *in-vacuo* to dryness, suspended in 100 ml of 33% Me_2NH/EtOH and stirred overnight at room temperature.

The solution was evaporated *in-vacuo* to dryness, dissolved in 50 ml of 20% K_2CO_3 and evaporated again *in-vacuo* to dryness. 50 ml of water were added to the residue and the solution, acidified with 37% HCl, was evaporated *in-vacuo* to dryness.

The crude residue and 10.8 ml (77.20 mmol) of TEA were dissolved in 50 ml of CH_2Cl_2, 50 ml of THF and 100 ml of CH_3CN.

3.00 g (22.20 mmol) of (S)-(-)-α-ethylbenzylamine, 0.78 g (5.78 mmol) of N-hydroxybenzotriazole (HOBT) and 11.9 g (57.90 mmol) of DCC were added and the solution was stirred at room temperature overnight.

The precipitated dicyclohexylurea was filtered off and the organic layer evaporated *in-vacuo* to dryness.

The brown oily residue was dissolved in 100 ml of CH_2Cl_2 and the precipitate was filtered off. The filtrate was extracted three times with 40% citric acid. The acqueous layer, basified with solid K_2CO_3, was extracted with CH_2Cl_2; the organic solution dried over Na_2SO_4 and evaporated *in-vacuo* to dryness afforded 10 g of a brown oil.

The crude product was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of *i*-Pr_2O/CH_2Cl_2 9 : 1 to afford 2.5 g of a white solid which was dissolved in toluene and left overnight.

The DCU precipitated was filtered and the solution, treated with ethanolic HCl, was evaporated *in-vacuo* to dryness. The crude product was recrystallized from a mixture of toluene/EtOH to yield 0.7 g of the pure title compound as colourless crystals.

$C_{28}H_{29}N_3O$·HCl
M.P. = 164-167 °C
M.W. = 460.02
$[\alpha]_D^{20}$ = + 25.3 (c = 1, MeOH)
I.R. (KBr): 3440; 3150; 3020; 2560; 2460; 1650; 1540 cm^{-1}.
300 MHz ^{1}H-NMR (DMSO-d_6; 353 K): δ 9.70 (s br, 1H); 8.10 (d, 1H); 7.85 (dd, 1H); 7.80 (s br, 1H); 7.70-7.10 (m, 12H); 5.15 (dt, 1H); 4.38-4.20 (m, 2H); 2.30 (s, 3H); 2.22 (s, 6H); 2.10-1.82 (m, 2H); 1.00 (t, 3H).
MS (EI; source 180 °C; 70 V; 200 mA): 423 (M+.), 380, 288.

EXAMPLE 113

(S)-N-(α-Ethylbenzyl)-3-methyl-7-methoxy-2-phenylquinoline-4-carboxamide

Prepared as described in Ex. 1, starting from 1.27 g (4.09 mmol) of crude 3-methyl-7-methoxy-2-phenylquinoline-4-carbonylchloride, 0.55 g (4.09 mmol) of (S)-(-)-α-ethylbenzylamine and 1.71 ml (12.27 mmol) of TEA in 24 ml of dry CH_2Cl_2 and 1 ml of DMF to help solubility. The reaction mixture was stirred 12 hours at room temperture.

After being concentrated *in-vacuo* to dryness, the residue was dissolved in CH_2Cl_2 (30 ml) and washed with 10% $NaHCO_3$, 5% citric acid and brine. The organic solution was dried over Na_2SO_4 and evaporated *in-vacuo* to dryness to obtain 1.87 g of a crude product, which was flash chromatographed on 230-400 mesh silica gel, eluting with a mixture of

hexane/EtOAc 70 : 30 to afford 0.350 g of a yellow oil.

$C_{27}H_{26}N_2O_2$
M.W. = 410.51
I.R. (KBr): 3240; 2965; 2930; 1635; 1535; 1220 cm^{-1}.

EXAMPLE 114

(S)-N-(α-Ethylbenzyl)-3-amino-5-methyl-2-phenylquinoline-4-carboxamide

0.75 g (2.64 mmol) of 3-amino-5-methyl-2-phenylquinoline-4-carboxylic acid were dissolved, under nitrogen atmosphere, in 30 ml of dry THF and 10 ml of CH_3CN.
0.38 g (2.83 mmol) of (S)-(-)-α-ethylbenzylamine and 0.69 g (5.18 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at -10°C.
0.61 g (2.97 mmol) of DCC, dissolved in 5 ml of CH_2Cl_2, were added dropwise and the solution was kept at -5°- 0°C for 2 hours, heated at 50 °C for 4 hours and then left at room temperature overnight.
The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and brine.
The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 10 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.
The solution was evaporated *in-vacuo* to dryness to obtain 0.86 g of a crude product which was flash chromatographed on 230-400 mesh silica gel, eluting with CH_2Cl_2/MeOH/conc. NH_4OH, 90 : 10 : 0.5 respectively, to afford 0.41 g of the title compound as an oil.
$C_{26}H_{25}N_3O$
M.W. = 395.50
I.R. (KBr): 3480; 3390; 3230; 3020; 1635; 1615; 1545 cm^{-1}.

EXAMPLE 115

(S)-N-(α-Ethylbenzyl)-3-methoxy-5-methyl-2-phenylquinoline-4-carboxamide

1.29 g (4.40 mmol) of 3-methoxy-5-methyl-2-phenylquinoline-4-carboxylic

acid were dissolved, under nitrogen atmosphere, in 40 ml of dry THF and 20 ml of CH_3CN.

0.63 g (4.62 mmol) of (S)-(-)-α-ethylbenzylamine and 1.13 g (8.36 mmol) of N-hydroxybenzotriazole (HOBT) were added and the reaction mixture was cooled at -10°C.

1.0 g (4.84 mmol) of DCC, dissolved in 5 ml of CH_2Cl_2, were added dropwise and the solution was kept at -5°- 0°C for 2 hours, heated at 50 °C for 4 hours and then left at room temperature overnight.

The precipitated dicyclohexylurea was filtered off and the solution evaporated *in-vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O, sat. sol. $NaHCO_3$, 5% citric acid, sat. sol. $NaHCO_3$ and brine.

The organic layer was separated, dried over Na_2SO_4 and evaporated *in-vacuo* to dryness; the residue was dissolved in 20 ml of CH_2Cl_2 and left overnight. Some more dicyclohexylurea precipitated and was filtered off.

The solution was evaporated *in-vacuo* to dryness to obtain 2.45 g of a crude product which was flash chromatographed on 230-400 mesh silica gel, eluting with hexane/EtOAc 7 : 2 containing 0.5% of conc. NH_4OH, to afford 0.28 g of the title compound as an oil.

$C_{27}H_{26}N_2O_2$

M.W. = 410.52

I.R. (KBr): 3270; 3020; 1635; 1535 cm^{-1}.

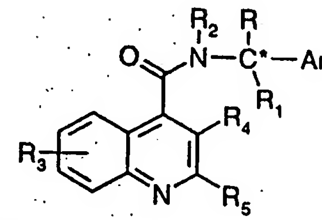
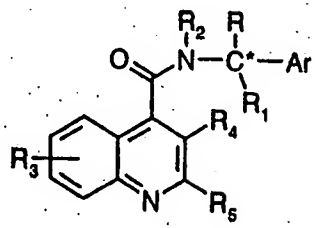


TABLE 6. Analytical data of compounds of Examples 93-115.

Ex.	Ar	R	R_1	R_2	R_3	R_4	R_5	*	Molecular formula	Melting point, ° C	[α]$_D^{20}$ c=0.5 MeOH
93	Ph	COOMe	H	H	H	H	Ph(4-Cl)	(R,S)	$C_{25}H_{19}ClN_2O_3$	170-172	--
94	Ph(4-OMe)	COOMe	H	H	H	H	Ph	(R)	$C_{26}H_{22}N_2O_4$	160-162	
95	Ph	COOMe	Me	Me	H	H	Ph	(R,S)	$C_{27}H_{24}N_2O_3$. HCl		--
96	Ph	COMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{20}N_2O_2$	160-161	--
97	Ph	CH_2CH_2OH	H	H	H	H	Ph	(R,S)	$C_{25}H_{22}N_2O_2$	167-169	--
98	Ph	Et	H	H	H	$OCH_2CH_2NMe_2$	Ph	(S)	$C_{29}H_{31}N_3O_2$. HCl	70 dec.[a]	--[b]
99	Ph	Et	H	H	H	NHCOMe	Ph	(S)	$C_{27}H_{25}N_3O_2$	268-269	- 71.4
100	Ph	Et	H	H	H	$OCH_2CH_2CH_2NMe_2$	Ph	(S)	$C_{30}H_{33}N_3O_2$. HCl	108 dec.	- 16.0
101	Ph	Et	H	H	H	OCH_2CH_2phthalimido	Ph	(S)	$C_{35}H_{29}N_3O_4$	172-175	- 16.3
102	Ph	Et	H	H	H	$OCH_2CH_2NH_2$	Ph	(S)	$C_{27}H_{27}N_3O_2$. HCl	119 dec.	- 19.4
103	Ph	Et	H	H	H	OCH_2CH_2pyrrolidino	Ph	(S)	$C_{31}H_{33}N_3O_2$. HCl	110-115	+ 4.5
104	Ph	Et	H	H	H	$NHCOCH_2NMe_2$	Ph	(S)	$C_{29}H_{30}N_4O_2$	189-191	- 63.1
105	Ph	Me	Me	H	H	OH	Ph	--	$C_{25}H_{22}N_2O_2$	166-169	--
106	Ph	Me	Me	H	H	NH_2	Ph	--	$C_{25}H_{23}N_3O$	166-168	--
107	Ph	Et	H	H	5-Me	H	Ph	(S)	$C_{26}H_{24}N_2O$	189-192	- 3.8

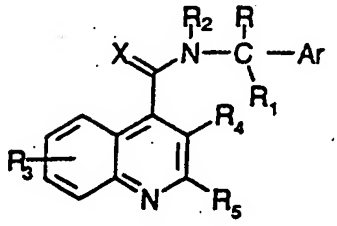
[a] free base: mp = 141-143; [b] free base: $[\alpha]_D^{20}$ = - 48.6 (c=0.5,MeOH)

TABLE 6. (continued)



Ex.	Ar	R	R_1	R_2	R_3	R_4	R_5	*	Molecular formula	Melting point ° C	$[\alpha]_D^{20}$ c=0.5 MeOH
108	Ph	CH(OH)Me	H	H	H	Me	Ph	(R,S)	$C_{26}H_{24}N_2O_2$	163-165	--
109	Ph	COMe	H	H	H	Me	Ph	(R,S)	$C_{26}H_{22}N_2O_2$	156-158	--
110	4-Py	Et	H	H	H	H	Ph	(R,S)	$C_{24}H_{21}N_3O$	218-219	--
111	2-thienyl	Et	H	H	H	H	Ph	(R,S)	$C_{23}H_{20}N_2OS$	134-137	
112	Ph	Et	H	H	H	CH_2NMe_2	Ph	(S)	$C_{28}H_{29}N_3O \cdot HCl$	164-167	+ 25.3
113	Ph	Et	H	H	7-MeO	Me	Ph	(S)	$C_{27}H_{26}N_2O_2$	oil	--
114	Ph	Et	H	H	5-Me	NH2	Ph	(S)	$C_{26}H_{25}N_3O$	oil	--
115	Ph	Et	H	H	5-Me	OMe	Ph	(S)	$C_{27}H_{26}N_2O_2$	oil	--

1. A compound, or solvate or salt thereof, of formula (I):



(I)

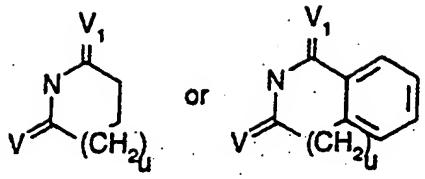
in which:

Ar is an optionally substituted phenyl, naphthyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted phenyl or phenyl C_{1-6} alkyl, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or is a group $-(CH_2)_p-$ when cyclized onto Ar, where p is 2 or 3.

R_1 and R_2, which may be the same or different, are independently hydrogen or C_{1-6} linear or branched alkyl, or together form a -(CH2)n- group in which n represents 3, 4, or 5; or R_1 together with R forms a group $-(CH_2)_q-$, in which q is 2, 3, 4 or 5.

R_3 and R_4, which may be the same or different are independently hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, mono- and di-C_{1-6} alkylamino, $-O(CH_2)_r-NT_2$, in which r is 2, 3, or 4 and T is hydrogen or C_{1-6} alkyl or it forms with the adjacent nitrogen a group



in which V and V_1 are independently hydrogen or oxygen and u is 0,1 or 2; $-O(CH_2)_s-OW_2$ in which s is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl; hydroxyalkyl, aminoalkyl, mono-or di-alkylaminoalkyl, acylamino, alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleus; or R_4 is a group $-(CH_2)_t-$ when cyclized onto R_5 as aryl, in which t is 1, 2, or 3;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

X is O, S, or N-C≡N.

2. A compound according to claim 1 in which:
Ar is phenyl, optionally substituted by C_{1-6} alkyl or halogen; thienyl or aC_{5-7} cycloalkdienyl group;

3. A compound according to claim 1 or 2 in which:
R is C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl or hydroxy C_{1-6} alkyl.

4. A compound according to any one of claims 1 to 3 in which:
R_1 and R_2 are each hydrogen or C_{1-6} alkyl.

5. A compound according to any one of claims 1 to 4 in which:
R_3 is hydrogen, hydroxy, halogen, C_{1-6} alkoxy or C_{1-6} alkyl.

6. A compound according to any one of claims 1 to 5 in which:
R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, halogen, aminoalkoxy, mono- or di-alkylaminoalkoxy, mono- or di-alkylaminoalkyl, phthaloylalkoxy, mono- or di-alkylaminoacylamino or acylamino;

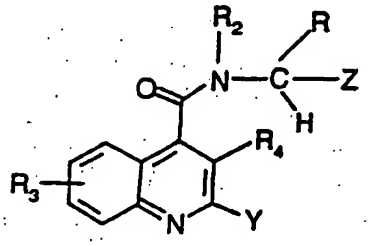
7. A compound according to any one of claims 1 to 6 in which:

R_5 is phenyl, thienyl, furyl, pyrryl or thiazolyl.

8. A compound of formula (I) according to claim 1, or a salt or solvate thereof, in which:

Ar is phenyl, 2-chlorophenyl, 2-thienyl or cyclohexadienyl;
R is methyl, ethyl, n-propyl, -COOMe, or -COMe;
R_1 and R_2 are each hydrogen or methyl;
R_3 is hydrogen, methoxy, or hydroxy;
R_4 is hydrogen, methyl, ethyl, methoxy, hydroxy, amino, chlorine, bromine, dimethylaminoethoxy, 2-(1-phthaloyl)ethoxy, aminoethoxy, 2-(1-pyrrolidinyl)ethoxy, dimethylaminopropoxy, dimethylaminoacetylamino, acetylamino, or dimethylaminomethyl;
R_5 is phenyl, 2-thienyl, 2-furyl, 2-pyrryl, 2-thiazolyl or 3-thienyl;
and X is oxygen.

9. A compound according to any one of claims 1 to 7, or a salt or solvate thereof, of formula (Ia)

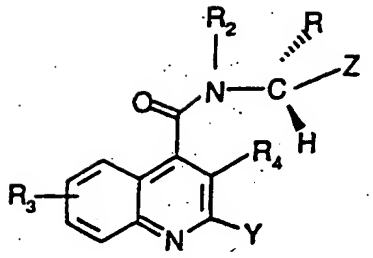


(Ia)

in which

R, R_2, R_3 and R_4 are as defined for formula (I), in any one of claims 1 to 7 and Y and Z, which may be the same or different, are each Ar as defined for formula (I) in claim 1 or 2.

10. A compound according to claim 9, of formula (Ib):



(Ib)

in which R, R_2, R_3 and R_4, Y and Z are as defined in claim 9.

11. A compound according to claim 1 selected from the group consisting of:

(R,S)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide;
(+)-(S)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide;
(-)-(R)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4 carboxamide;
(+)-(S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(-)-(R)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-7-methoxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-7-hydroxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(carboxy)benzyl]-7-methoxy-2-phenylquinoline-4-carboxamide hydrochloride;
(R,S)-N-[α-(methylaminocarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-thienyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-furyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-pyridyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)-2-thienylmethyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonylmethyl)benzyl]-2-phenylquinoline-4-

carboxamide;
(-)-(R)-N-[α-(methoxycarbonyl)-1,4-cyclohexadienylmethyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(1-hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide single diast;
(R,S)-N-(α-ethylbenzyl)-3-methoxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-n-butyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]benzo-1,3-cycloheptadieno[1,2-b]quinoline-8-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-hexyl-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide;
(+)-(R)-N-(α-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-methoxyphenyl)quinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-phenyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-fluorophenyl)quinoline-4-carboxamide;
(R,S)-N-[α-(ethyl)-3,4-dichlorobenzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(hydroxymethyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-7-chloro-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-6-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxymethyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-6-chloro-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-3-ethyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-n-propylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-ethyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-phthalimido-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-n-propyl-2-phenylquinoline-4-carboxamide;

(-)-(S)-N-(α-ethylbenzyl)-6-bromo-3-methyl-2-(4-bromophenyl)quinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-6-bromo-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-6-methoxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-benzofuryl)quinoline-4-carboxamide;
(R,S)-N-[(1,2-diphenyl)ethyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-trifluoromethylbenzyl)-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-methoxy-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-ethyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(ethyl)-4-chlorobenzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-N-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(3-thienyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-5,6-dihydrobenzo[a]acridine-7-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-pyrryl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-thiazolyl)quinoline-4-carboxamide;
(R,S)-N-(1-indanyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-n-butylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-methylphenyl)quinoline-4-carboxamide;
(R,S)-N-(α-heptylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-methylphenyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-methoxyphenyl)quinoline-4-carboxamide;
N-(1-phenylcyclopentyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-hydroxyphenyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(3,4-methylendioxyphenyl)quinoline-4-carboxamide;
N-(α,α-dimethylbenzyl)-2-phenylquinoline-4-carboxamide;

(R,S)-N-[α-(ethyl)-4-methylbenzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(3-pyrryl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(3,4-dichlorophenyl)quinoline-4-carboxamide;
(-)-(R)-N-[α-(aminomethyl)benzyl]-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-chloro-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-bromo-2-phenylquinoline-4-carboxamide;
(R,S)-N-(α-*iso*-propylbenzyl)-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-2-phenylquinoline-4-carboxamide;
(+)-(R)-N-(α-ethylbenzyl)-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-6-fluoro-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-cyclohexylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(3-chlorophenyl)quinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-chlorophenyl)quinoline-4-carboxamide;
(R,S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-8-acetyloxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-8-hydroxy-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2,4-dichlorophenyl)quinoline-4-carboxamide;
(-)-(R)-N-[α-(methoxycarbonyl)-4-hydroxybenzyl]-2-phenylquinoline-4-carboxamide hydrochloride;
N-diphenylmethyl-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide;
(+)-(R)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide;
(-)-(R)-N-[α-(methoxycarbonyl)benzyl]-3-hydroxy-2-phenylquinoline-4-carboxamide;
(-)-(R)-N-[α-(dimethylaminomethyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(dimethylaminocarbonyl)benzyl]-2-phenylquinoline-4-

carboxamide;
(R,S)-N-[α-(aminocarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(1-pyrrolidinylcarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(-)-(R)-N-[α-(carboxy)benzyl]-2-phenylquinoline-4-carboxamide hydrochloride;
(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-chlorophenyl)quinoline-4-carboxamide;
(R)-N-[α-(methoxycarbonyl)-4-methoxybenzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methoxycarbonyl)-α-(methyl)benzyl]-N-methyl-2-phenylquinoline-4-carboxamide hydrochloride;
(R,S)-N-[α-(methylcarbonyl)benzyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(2-hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-(2-dimethylaminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride;
(-)-(S)-N-(α-ethylbenzyl)-3-acetylamino-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-3-(3-dimethylaminopropoxy)-2-phenylquinoline-4-carboxamide hydrochloride;
(-)-(S)-N-(α-ethylbenzyl)-3-[2-(1-phthaloyl)ethoxy]-2-phenylquinoline-4-carboxamide hydrochloride;
(-)-(S)-N-(α-ethylbenzyl)-3-(2-aminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride;
(+)-(S)-N-(α-ethylbenzyl)-3-[2-(1-pyrrolidinyl)ethoxy]-2-phenylquinoline-4-carboxamide hydrochloride;
(-)-(S)-N-(α-ethylbenzyl)-3-(dimethylaminoacetylamino)-2-phenylquinoline-4-carboxamide;
N-(α,α-dimethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide;
N-(α,α-dimethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide;
(-)-(S)-N-(α-ethylbenzyl)-5-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(1-hydroxyethyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(methylcarbonyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(ethyl)-4-pyridylmethyl]-2-phenylquinoline-4-carboxamide;
(R,S)-N-[α-(ethyl)-2-thienylmethyl]-2-phenylquinoline-4-carboxamide;
(+)-(S)-N-(α-ethylbenzyl)-3-dimethylaminomethyl-2-phenylquinoline-

4-carboxamide hydrochloride;

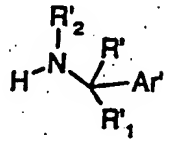
(S)-N-(α-ethylbenzyl)-3-methyl-7-methoxy-2-phenylquinoline-4-carboxamide;

(S)-N-(α-ethylbenzyl)-3-amino-5-methyl-2-phenylquinoline-4-carboxamide;

(S)-N-(α-ethylbenzyl)-3-methoxy-5-methyl-2-phenylquinoline-4-carboxamide;

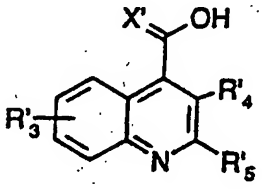
12. A compound according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

13. A process for preparing a compound of formula (I) as defined in any one of claims 1 to 12, or a solvate or salt thereof which comprises reacting a compound of formula (III)



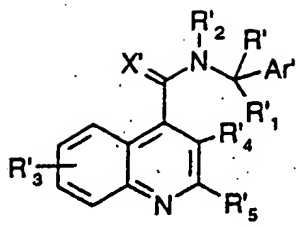
(III)

in which R', R'_1, R'_2 and Ar' are R, R_1, R_2 and Ar as defined for formula (I) or a group or atom convertible to R, R_1, R_2 and Ar, with a compound of formula (II)



(II)

or an active derivative thereof, in which R'_3, R'_4, R'_5 and X' are R_3, R_4, R_5 and X as defined for formula (I) or a group convertible to R_3, R_4, R_5 and X, to form a compound of formula (Ic)



(Ic)

and optionally thereafter performing one or more of the following steps:

(a) where R', R'_1 to R'_5, Ar' and X' are other than R, R_1 to R_5, Ar and X, converting any one of R', R'_1 to R'_5, Ar' and X' to R, R_1 to R_5, Ar and X to obtain a compound of formula (I),

(b) where R', R'_1 to R'_5, Ar' and X' are R, R_1 to R_5, Ar and X, converting any one of R, R_1 to R_5, Ar and X to another R, R_1 to R_5, Ar and X, to obtain a compound of formula (I),

(c) forming a salt and/or solvate of the obtained compound of formula (Ic).

14. A process according to claim 13 in which the active derivative of the compound of formula (II) is an acid halide.

15. A pharmaceutical composition comprising a compound of formula (I) or salt or solvate thereof, as defined in any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

16. A compound of formula (I), or a solvate or salt thereof, as defined in any one of claims 1 to 12, for use as an active therapeutic substance.

17. A compound of formula (I), or a solvate or salt thereof, as defined in any one of claims 1 to 12, for use in treating pulmonary disorders (asthma, chronic obstructive pulmonary diseases -COPD-, airway hyperreactivity, cough), skin disorders and itch (for example, atopic dermatitis and cutaneous wheal and flare), neurogenic inflammation and CNS disorders (Parkinson's disease, movement disorders, anxiety and psychosis), convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression.

18. An NK_3 receptor antagonist for use in the treatment of convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression.

19. Use of a compound of formula (I), or a solvate or salt thereof, as defined in any one of claims 1 to 12 in the manufacture of a medicament for use in the treatment of pulmonary disorders (asthma, chronic obstructive pulmonary diseases -COPD-, airway hyperreactivity, cough), skin disorders and itch (for example, atopic dermatitis and cutaneous wheal and flare), neurogenic inflammation and CNS disorders (Parkinson's disease, movement disorders, anxiety and psychosis), convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression.

20. Use of an NK_3 receptor antagonist in the manufacture of a medicament for use in the treatment of convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression.

21. A method for the treatment and/or prophylaxis of pulmonary disorders (asthma, chronic obstructive pulmonary diseases -COPD-, airway hyperreactivity, cough), skin disorders and itch (for example, atopic dermatitis and cutaneous wheal and flare), neurogenic inflammation and CNS disorders (Parkinson's disease, movement disorders, anxiety and psychosis), convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression in mammals, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I), or a solvate or salt thereof, as defined in claim 1.

22. A method for the treatment and/or prophylaxis of convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression in mammals, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of an NK_3 receptor antagonist.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 95/02000

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/52 A61K31/47 C07D409/04 C07D405/04 C07D401/04
C07D409/12 C07D221/18 C07D417/04 C07D401/12 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	No relevant documents disclosed -----	

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 1995	28.08.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/02000

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21 and 22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.